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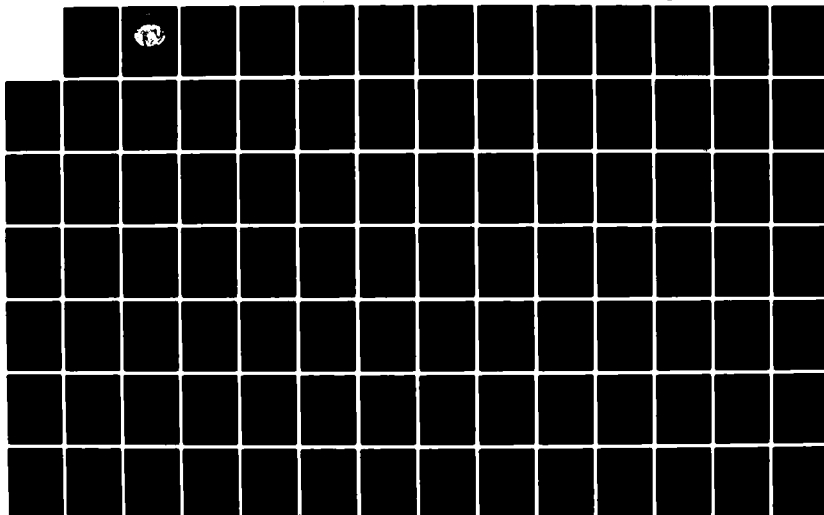
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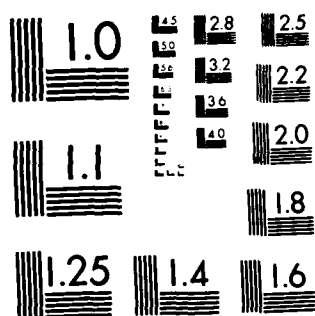
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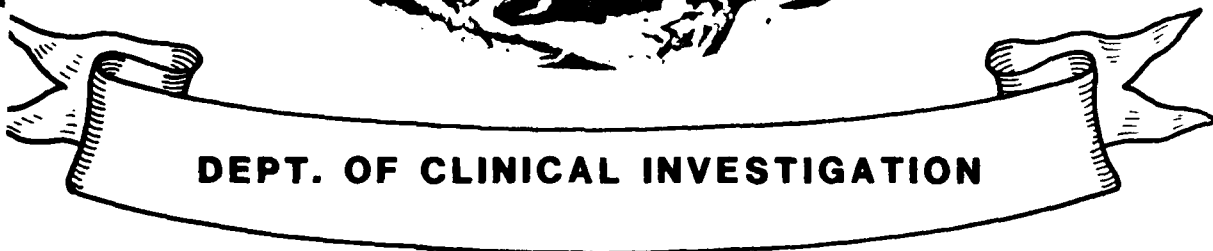


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20. ABSTRACT (Continue on reverse side if necessary and identify by block number) This report serves to detail the progress, status, and funding of approved projects conducted under protocol by staff members, interns, and residents at William Beaumont Army Medical Center. The varying projects as reported are classified according to the service or department to which the principal investigator belongs. Research conducted at WRAMC is categorized as either basic experimental medicine or trials and testing of clinical medicine procedures using the indigenous population for which this medical facility provides support.		

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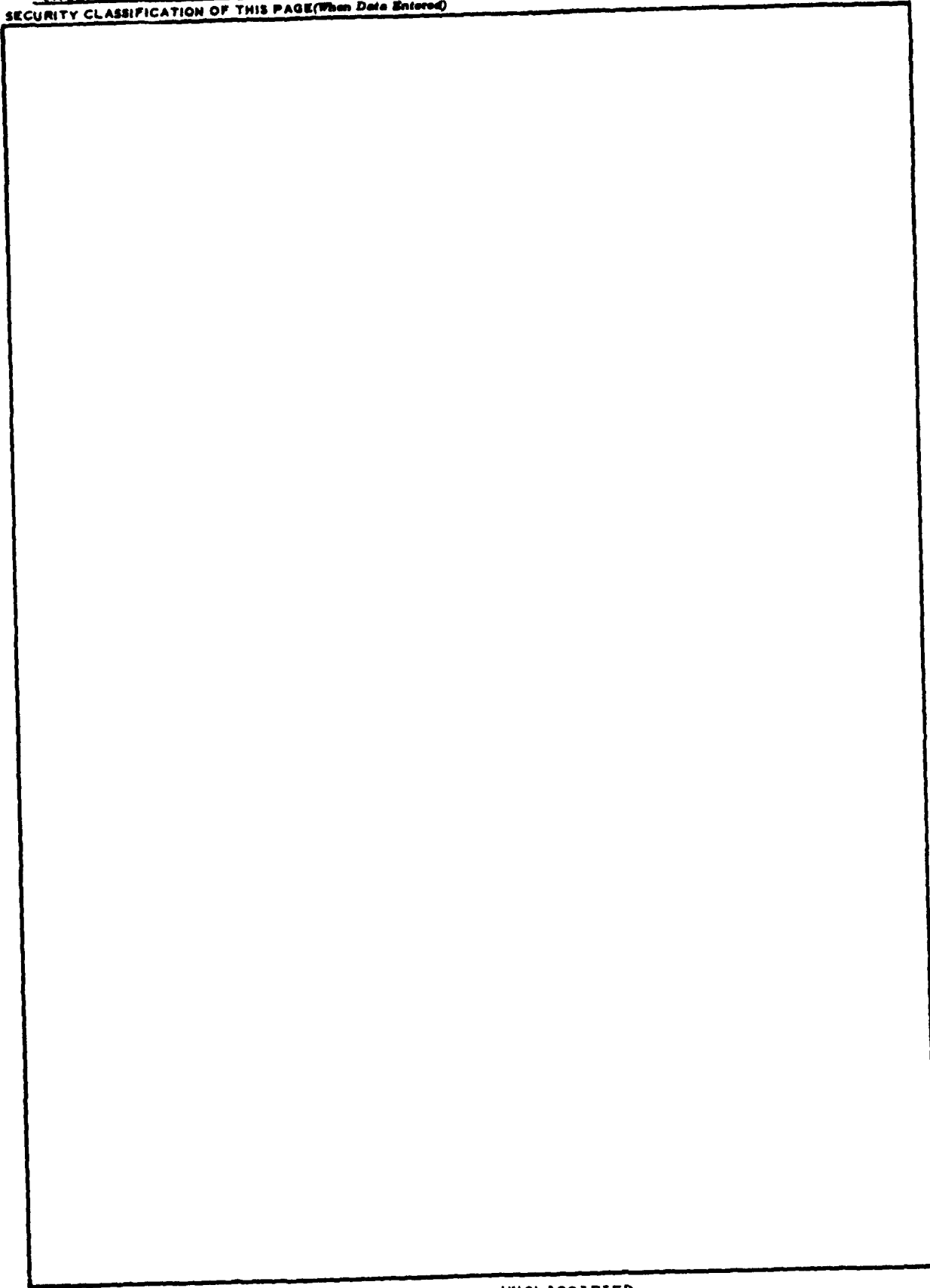
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## FOREWORD

The Department of Clinical Investigation, formerly Medical Research and Development, is entering its 18th year of operation. There have been nadirs but, overall, the history is one of gradual progress and expansion. This has occurred despite the disadvantageous position of WBAMC among its fellow MEDCENs and, importantly, at a time when the demise of clinical investigation and the clinical investigator is bemoaned extensively in academic medicine. As addressed at length elsewhere by the undersigned, the impetus to overcome this perceived shortfalling through revised accreditation standards and organizational goals impacts on our mission. However unique opportunity continues to exist within the Army Medical Department as does the potential for meeting the foreseeable challenges.

The young physician, nurse, PhD, psychologist, dentist, veterinarian or other biomedical scientist in the Army serves in an environment where patient care demands are enormous, but also where commitment to excellence and an atmosphere of inquiry coexist. As the Medical Corps, and other Corps, gain adequate manpower and stability, the dedicated teachers and researchers within those Corps can increasingly expose these young intellects to scientific methods. Controlled observation should be at least understood, and preferably applied as widely as possible.

Further progress in decentralization of protocol approval occurred in FY82. Drug company sponsored IND studies may now be approved locally. The Departmental growth in OMA budget and equipment continued, but space constraints have become critical. Despite gaining seven new recognized requirements on an Interim Schedule X since the last manpower survey, fewer personnel are assigned as of the date of this writing (Dec 82) than before the survey. Nevertheless, new protocols were accepted in large numbers and the largest numbers of completed protocols and refereed or thesis publications/presentations in our history were achieved, including a record number directly resulting from formal protocols. Gratifyingly, and appropriately, involvement in Clinical Investigation has disseminated throughout the Command, and continues to do so. We are confident the leadership will recognize the need to broaden our support base in this enterprise. Unfortunately, we were unable to complete several protocols and the largest number of terminated protocols occurred. The staff of the DCI is to be especially commended as are the investigators who actively pursued their projects, frequently utilizing their own hours from off-duty time. All investigators for each work unit are identified in the respective reporting sections. Without additional space and personnel, the Department will be forced to restrict acceptance of meritorious protocols, an obviously counterproductive measure.



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The contributions of the many nurses, technicians, corpsmen administrative personnel and patient volunteers, who are vital to the successful implementation of clinical research projects, are appreciated. The committee members providing the critical review imperative in the proper conduct of our mission are acknowledged on Page 5.

I am grateful for the editorial and typographical assistance of Ms Peggy Casteel in the completion of this document. Mr. Shel Chaplain, ARC volunteer, has donated one day per week of general duties again this year, and I thank him for his efforts.



L.L. PENNEY, M.D.  
COL, Medical Corps  
C, Dept Clinical Investigation

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## PUBLICATIONS AND PRESENTATIONS

### Department of Clinical Investigation

Lock JP, Penney LL, Jawadi MH, Betz G. Isolated gonadotropin deficiency in three sisters. Accepted for publication in *Obstet Gynecol*

Killam AP, Penney LL: The administration of steroids for fetal lung maturity. Chapter in *Controversy in Obstetrics and Gynecology*, W.S. Saunders Co. (C)

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renal failure (ARF) in patients with pre-existing chronic renal failure (CRF). Presented at the Amer Soc Nephrology 14th Ann Meeting, 22 Nov 81 (C)

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Academy of Health Sciences, Anesthesiology for ANC Officers Course (C).

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Reamy K, White SE, Daniell WC, LeVine ES: Sexuality and pregnancy. A prospective Study. J Reprod Med 27:321, 1982.

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#### Department of Pathology

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#### Department of Pediatrics

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Butler AB, Scott RM, Schydlower M, Lampe RM, Schwab JA, Muelenaer AA: The immunoglobulin response to reimmunization with rubella vaccine. J Pediatrics 99:531-534, 1981 (C).

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Walker WO: Thyroid carcinoma in a pediatric military dependent population. Presented at the Texas Pediatric Society Meeting, Sept 82 (First prize paper for Resident essay).



Walker WO: A diagnostic approach to liver masses: The role of abdominal computerized tomography. Accepted for publication in Military Medicine.

Weir MR, Patterson HS: Tube size, lavage, and emesis. Ltr to the Editor, Pediatrics 69:388, 1982.

Weir MR: Things that go damp in the night. Accepted for publication in Mil Med.

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#### Department of Surgery

Camunas JA, Butler AB, Butler JE: Adolescent Trauma - the impact of the motorcycle. Presented at the Soc Adolescent Medicine Meeting, Oct 81, New Orleans, La (C).

Cavanaugh D, Butler J, Gaines T: Traumatic avulsion of the inferior vena cava from the right atrium. Accepted for publication in Military Medicine.

Cavanaugh D, Livaudais W, Paris J, Greer TM:: Pericardial rupture with complete luxation of the heart. Accepted for publication in Mil Med

Diaz-Ball F. Intraoperative aid for diagnosis of renal masses. Presented at the James C. Kimbrough Urological Seminar, Aurora CO, 16-20 Nov 81.

Diaz-Ball F: A safer way to catheterize the tortuous urethra. Presented at the James C. Kimbrough Urological Seminar, Aurora CO, 16-20 Nov 81.

Diaz-Ball F, Otterson W, Boyce D, Staifford J: A new technique for interval management of vesico-vaginal fistula. Presented at the James C. Kimbrough Urological Seminar, Aurora CO, 16-20 Nov 81.

Hardy MR: Comparison of direct and indirect radionucleotide cystography with x-ray evaluation of vesicoureterl reflux. Presented at the James C. Kimbrough Urological Seminar, Aurora CO, 16-20 Nov 81.(C)

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## UNIT SUMMARY

### OBJECTIVES

The Department of Clinical Investigation, William Beaumont Army Medical Center, was established 2 February 1965 as the Medical Research and Development Service. Following reorganization and official recognition under AR 40-38 (23 Feb 73) the service became the Clinical Investigation Service. Departmental status was achieved in FY80. The mission is to promote, conduct, and coordinate clinical and directed basic research. The policies and objectives are outlined in Department of Defense Directive Number 6000.4 dated 7 April 1971:

"Clinical investigation is an essential component of optimum medical care and consists of the organized inquiry into clinical health problems, for the following purposes:

1. To achieve continuous improvement in the quality of patient care.
2. To provide experience in the mental discipline achieved by participation in such organized inquiries, and to provide experience for personnel who will ultimately be teaching chiefs in military hospitals and medical specialty consultants.
3. To maintain an atmosphere of inquiry because of the dynamic nature of the health sciences.
4. To maintain high professional standing and accreditation of advanced health education programs."

Item number 4 continues to be critical in the wake of the GMENAC recommendations and the move to reduce the number of training programs. WBAMC is particularly vulnerable as this institution is essentially free-standing and for several years suffered absolute and relative physician and allied scientist understaffing.

The Department supports in-house research projects by AMEDD staff members, residents, and interns of all Corps, assisting in the formulation, preparation, and promulgation of research protocols; in the performance of the studies, and finally in the review and publication of results. The Department furnishes experimental design and statistical and technical expertise; develops and carries out special laboratory procedures; and provides general support in terms of equipment, supplies, and animal resources when required. Through contractual services in FY82 the department has continued to provide enhanced statistical support, at the PhD level, to

investigators at WBAMC. The creative and inspirational environment and technical knowledge available serve to stimulate the undertaking of basic and clinical medical and paramedical research at William Beaumont Army Medical Center by staff members, and interns and residents in training, as well as provide a basic instructional facility to elucidate the principles and conduct of research.

In addition to the primary mission, as stated above, the department is active in supporting several training and teaching programs involved with direct patient care. For example, the Biological Research Service directly supports approximately 450 anesthesia and surgical assistance training procedures annually ranging from minor suturing techniques for the Clinical Specialist Course students through aortic bypass grafts for the surgical residents. Examples of formal training protocols supported by the department were detailed in FY80. The current projects are available upon request.

The Department of Clinical Investigation has provided scientific and administrative computational support to the Departments of Nursing, Pathology, Medicine, Surgery, and Logistics Division of WBAMC. The department provides this support as it possesses unique skills and equipment necessary to perform the tasks. The tasks may require mathematical modeling, statistical analysis, or graphical representations.

In addition, all radioimmunoassay calculations and reports performed by Nuclear Medicine were done utilizing equipments and programs provided by the Department of Clinical Investigation.

#### TECHNICAL APPROACH

The Department of Clinical Investigation provides support for staff research projects under the guidelines of the Declaration of Helsinki, Clinical Investigation Program (AR 40-38), HSC Reg 40-2, and the Use of Investigational Drugs in Humans and the Use of Schedule I Controlled Drug Substances (AR 40-7). Research is conducted under protocols approved by the Research Committee (WBAMC HR 70-4), the Human Use Committee (WBAMC HR 40-38) and the Radioisotope Committee (WBAMC HR 40-37) where applicable. In those research protocols utilizing laboratory animals, the investigators follow guidelines set forth in "Guide for Laboratory Animal Facilities and Care," published by the Committee on the Guide for Laboratory Animal Facilities and Care of the Institute of Laboratory Animal Resources, National Academy of Sciences-National Research Council, and the criteria established by the American Association for Accreditation of Laboratory Animal Care.

# MANPOWER

<u>Title</u>	Recognized Requirement (SSI/MOS)	Auth	Assigned	Name
Chief	60 J9A	0-6	0-6	Penney, L.L.
Biochemist/ Office of Chief	68 C00	0-3	0-3	Smith, M.L.
Biochemist/ Chem Svc	68 C00	0-3	-	--
Immunologist/ Microb Svc	68 E00	-	0-3	Serio, C.S.
Vet Lab Anm Off	64 C	0-3	0-3	O'Brien, A.W.
Med Lab NCO	92 B30	-	-	--
Biochem Sci Asst	01H20	E-5	-	
Vet Anm Sp	91T20	E-5	-	
Biochem Sci Ass	01H20	E-5	E-5	Morales, J.A.
Vet Anm Sp	91T20	-	-	--
Vet Anm Sp	91T10	E-4	-	
Vet Anm Sp	91T10	E-3	E-4	Jamison, J.J.
Vet Anm Sp	91T10	E-3	E-3	Chase, T
Hlth Tech/ Anm Res Asst	00699	GS-7	GS-7	Revels, J.E.
Anm Caretaker	07706	WG-3	WG-1	Burton, A.D.
Chemist	01311	GS-12	GS-12	Rauls, D.O.
Microbiologist	00403	GS-12	GS-12	Frederick, R.J.
Chemist	01320	GS-9	GS-9	Sandison, S.W.
Immunochemist	01320	GS-9	-	
Med Lab Tech	00645	GS-7	GS-7	Manna, B.S.
Med Lab Tech	00645	GS-7	GS-6	Crouch, S.K.
Med Lab Tech	00645	GS-7	GS-6	Martin, S.
Med Lab Tech	00645	-	-	--
Electron Micr Tech	00699	-	-	--
Med Lab Aide	00645	-	-	--
Editorial Asst	01087	GS-7	GS-7	Casteel, P.J.
Clerk Typist	00322	GS-4	GS-4	Turner, L.

Note that the DCI is operating at 63% of recognized requirements. It should also be noted that the military contingent in the Biological Research Svc is at 50% recognized requirements. Lack of effective research is again occurring from the hiatus created. Additional authorizations for newly recognized requirements and additional recognized requirements will be critical.

EXPENDITURES	FY79	FY80	FY81	FY82
Personnel (Civilian)	151,769	171,444	198,298	191,190
Consumable Supplies	34,392	60,134	86,351	122,189
MEDCASE Equipment	37,333	140,868	203,884*	77,965
Capital Equipment	2,425	10,427	36,256	34,144
TDY	1,179	1,469	2,387	4,743
Contracts, Services, Printing & Reproduction	2,116	2,494	5,905	2,982
TOTAL	\$229,214	386,836	531,081	433,213
Military Pay	141,385	167,437	217,503	259,726
	\$370,599	\$554,273	\$748,584	\$692,939

\*The MEDCASE expenditure includes a year-end supplement of \$85,000 for a cell sorter. The Dept Clinical Investigation further accounted the supply expenditures into general office \$4,481; general laboratory (divided among two or more protocols or for maintenance, standards, etc) \$29,319; and general biologic research facility (primarily training protocols) \$10,780. The remaining \$77,609 was spent on 32 specific protocols and the amount is noted under OMA cost on the appropriate detail sheets. The figures are annual for FY82, and, in parentheses, accumulative. Also included in this \$77,609 were expenses required to establish new services of immunology and tissue culture support within the department. Major equipment purchased specifically for a given protocol is accounted under MEDCASE for that protocol. Most equipment is for diverse uses and cannot be accounted on individual protocols.

It is impossible to account equipment, personnel, TDY and general supplies to specific protocols. However eliminating terminated protocols, there were 112 active protocols in FY81. The following figures will be high estimates because a portion of personnel, supply, and equipment expense is for training as opposed to research. Furthermore, all of the salary for the C, Dept Clinical Investigation is accounted here and a portion of his time is actually spent in patient care and teaching.

Comptroller data listing of \$692,939, indicates an overall average of \$6,187 total expenditure per active protocol. Several of the older protocols received more limited funding in deference to those more current. It is also important to note that a large clinical study, with little or no equipment or laboratory expense, can be quite costly in terms of personnel for administration, data collection, and reduction, committee preparation, annual review, HSC and OTSG coordination and manuscript preparation. The average personnel cost for these services exceeds \$500 per protocol for the WBAMC DCI. Partly due to the avalanche of regulations and increasing numbers of forms, minutes, etc., which must be maintained and distributed, the supply costs for paper, clips, staples, folders, and other strictly administrative materials have risen to an average of \$40 per active protocol per year.

TDY for minimal continuing education and mission-essential training was granted. The department was included in the approval process for TDY to present papers from protocols. Funds available were \$21,000 .

The numbers of protocols accepted, the increased number completed, and the increase in publications and presentations continue to attest to the value of DCI staff stabilization as noted in the FY78 report. Stabilization of principal investigators is improving. These facts, plus funding and equipment postures are partially responsible for another large annual increase in the number of new protocols. Again, several of these ongoing protocols are extremely ambitious and reflect both internal vigor and external pressures.

PROGRESS: During this fiscal year WBAMC authors had 88 articles accepted for national/regional presentation or publication. This list begins on page 20. Nearly one-half of these publications and/or presentations resulted directly from protocols (C). It is important to note the DCI provided editorial and/or statistical assistance on many of the remainder. A tabulation of pertinent workload and dispositions compared to budget (not adjusted for inflation) for the past seven years follows: (FY77 and 7T have been combined, but adjustment to 12 months is shown in parentheses) The final chart is a summary of protocol dispositions per year of origination. The SWOG principal investigator at WBAMC resigned forcing termination of many protocols. Newly assigned personnel are seeking affiliation with an alternate group as SWOG is apparently not accepting new principal investigators.

	Protocols Ongoing 1 Oct	New Protocols Submitted During FY	Total Protocols	Protocols Completed During FY	Protocols Terminated During FY	Publications and Presentations	NMA Budget
FY76	49	32	81	12	16	48	\$20,471
FY77 & 77T	53 (42)*	25 (20)	78 (62)	18 (14)	15 (12)	24 (19)	\$56,831 (\$45,465)
FY78	45	30	75	3	9	28	\$35,923
FY79	63	43	106	9	14	46	\$34,392
FY80	83	41	124	25	25	63	\$60,134
FY81	74	59	133	16	17	80	\$86,351
FY82	100	58	158	42	45	88	\$122,189
FY83	71						

\*Figures in parentheses represent adjustment to a base of 12 months.

Protocol Disposition Per Year of Origination

<u>FY</u>	<u>Completed</u>	<u>Terminated</u>	<u>Ongoing</u>
FY76		1	1
FY77	2	2	1
FY78	2		1
FY79	3	5	
FY80	13	15	2
FY81	11	19	21
FY82	<u>11</u>	<u>3</u>	<u>45</u>
TOTAL	42	45	71



# Detail Summary Sheet

Date: 1 Oct 82 Prot No:78/15 Status: Completed

## Title:

Penicillin Alone vs Ampicillin and Gentamicin in the Treatment of Group B Streptococcal Sepsis

Start Date: 1978 Est Comp Date: Mar 1982

Principal Investigator: Facility:

R.J. Frederick, PhD, DAC

Dept/Sec: Microbiology Svc, DCI Assoc Investigators

## Key Words:

Streptococci; antimicrobial agents

Accumulative MEDCASE	Est	Periodic
Cost	OMA Cost:FY81 and	Review Results
Study Objective	(Accumulative)\$0(2732)	

To determine the in vivo and in vitro killing rates of these antibiotics.

## Technical Approach:

Scintillation counting will be used for in vitro studies. Serial blood cultures will be used for in vivo studies with a rabbit model.

## Progress:

In vivo responses to penicillin tolerant strains of group B streptococci were monitored in the rabbit model for early-onset streptococcal sepsis. New Zealand white rabbits were injected intravenously with cell suspensions of radiolabeled, log phase bacteria with and without a three-hour exposure to penicillin. Clearance rates were monitored by measuring the disappearance of radiolabel from blood samples taken in a continuous sampling technique at ten second intervals. Clearance rates were measurably different (See Table 1) with the treated cells having nearly double the  $t_{1/2}$  of untreated cells. Pre-immunization of the animals resulted in an increase in  $t_{1/2}$  of untreated bacteria while that of the treated bacteria decreased.

Table 1. Clearance rates of penicillin treated and untreated group B streptococci.

GROUP B STREPTOCOCCI TYPE 1a (BAMC 11)  
IN VIVO CLEARANCE RATES

CULTURE	IMMUNIZED	SLOPE	t <sub>1/2</sub> (Sec)
LOG PHASE	-	-0.0070	46
	+	-0.0052	64
PENICILLIN* TREATED	-	-0.00334	82
	+	-0.0077	41

\*150 units/ml for three hours at 37°C

Previous work demonstrated the continued morphological integrity of the bacteria after a three hour exposure to penicillin. Although the structural integrity is maintained and only a ten percent loss of cell viability occurs, cell wall constituents are released and the average cell diameter increases approximately 20 percent.

#### PROGRESS

The bacterial strain used in this study was a clinical isolate. This particular strain was found to be penicillin tolerant (i.e. MBC/MIC of more than 32), explaining previous observations on the effects of this antibiotic in the streptococcal culture. Laboratory experiments have been completed and the data are being finalized for presentation and consideration for future work under a new protocol.

# Detail Summary Sheet

Date: 1 Oct 82 Prot No: 79/01 Status: Completed  
Title:

Role of Deoxyribonucleic Acid Attachment to Cell Membrane in the Regulation of Bacterial Growth

Start Date: 1979 Est Comp Date: Sept 1982  
Principal Investigator: Facility:

R.J. Frederick, PhD, DAC

Dept/Sec: Microbiology Svc, DCI Assoc Investigators  
Key Words:

Deoxyribonucleic acid; cell membrane

Accumulative MEDCASE Cost	Est OMA Cost: \$195(3357)	Periodic Review Results
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Study Objective:

To isolate and examine specific deoxyribonucleic acid (DNA) sequences associated with bacterial cytoplasmic membranes.

## Technical Approach:

Our initial experiments are designed to analyze the effect of different restriction enzymes on isolated nucleoids. These are the folded chromosome of the bacteria which can be isolated in their compact state while retaining the membrane association. The procedure can be done simply with reasonable yields under salt and pH conditions which will facilitate endonuclease treatments. Once isolated, the tritium labeled nucleoids (i.e. the entire chromosomes) will be digested with commercially available restriction endonucleases. These enzymes cleave the DNA molecules at specific nucleotide sequences resulting in specific fragments which can subsequently be separated by agarose gel electrophoresis and resolved on x-ray film by autoradiofluorography. Membrane associated fragments will be purified by fractionation using the magnesium-sarkosyl crystal separation technique. The fragments will be recovered by standard techniques and analyzed by agarose gel electrophoresis. Once the specific sequences have been resolved, we will begin to identify what regions of the chromosome are involved and under what conditions. The relationship of the attachment to bacterial growth may then be examined by varying the growth conditions of the organisms, using appropriate mutant strains and in the presence of various antibiotics.

**PROGRESS:**

Quantitative and qualitative differences between membrane associated and free restriction fragments have been demonstrated. Three different enzymes have to be used to produce confirmatory results. Further analyses of the membrane associated DNA sequences will be pursued under a separate protocol.

Detail Summary Sheet

Date: 1 Oct 82      Prot No: 79/07      Status: Terminated  
Title:

Synthesis of Inhibitors of the Shikimate Pathway for Investigation  
As Potential Antimicrobial Agents

Start Date: 1979      Est Comp Date: Sep 82  
Principal Investigator:      Facility:

D.O. Rauls, PhD, DAC

Dept/Sec: Chemistry Svc, DCI      Assoc Investigators  
Key Words:

Shikimate; Antimicrobial agents

Accumulative MEDCASE	Est	Periodic
Cost	OMA Cost:0(\$1546)	Review Results

Study Objective:

The 6-alpha and 6-beta fluoro analogs of shikimic acid will be synthesized as potential irreversible inhibitors of the pathway responsible for aromatic acid synthesis in microorganisms. The compounds will then be evaluated for antibacterial activity using a standard antibacterial screen.

Technical Approach:

The desired 6-fluoro analogs of shikimic acid will be synthesized by established synthetic techniques. The antimicrobial activity will be determined using standard assays. The anticipated limiting factors appear to be related to the potential lability of the products.

Progress:

Personnel shortages precluded further work on this protocol.

# Detail Summary Sheet

Date: 1 Oct 82 Prot No: 80/3 Status: Terminated

## Title:

Maternal Serum and Urinary Steroid Concentrations During Contraction Stress Testing

Start Date: 1 Oct 81

Est Comp Date: 1983

Principal Investigator:

Facility:

L.L. Penney, COL, MC

Dept/Sec: C, Dept Clinical Invest

Assoc Investigators

## Key Words:

Cortisol; Estriol; Oxytocin

Accumulative MEDCASE

Est

Periodic

Cost

OMA Cost:

Review Results

## Study Objective:

To determine if any changes occur in maternal serum steroid concentrations during contraction stress testing, and if so, are they of predictive value in regard to fetal outcome.

## Technical Approach:

All patients admitted for contraction stress testing will be asked to participate. A two-hour urine specimen prior to beginning and another immediately from starting the oxytocin will be collected. Three to five cc of venous blood will be drawn from the arm opposite the IV infusion at 0,30,60,90 and 120 minutes of the test. The blood will be drawn in three 1 cc aliquots from the same venipuncture at five minute intervals around each drawing time and the serum combined in equal volume to compensate known variabilities in serum estriol. Specimens will be analyzed for unconjugated and total estriol and an aliquot frozen for possible analyses of cortisol, <sup>16</sup>OH progesterone and other steroids which are being proposed as indicators of fetal well being. All specimens from positive, equivocal, or, in retrospect, false negative tests, will be analyzed following randomization assignment. Twenty negative studies will be used to compare mean urinary and serum levels at each time period from controls and study group patients. Any significant differences will be correlated in an attempt to define equivocal, false positive and false negative results.

## Progress:

None.

Detail Summary Sheet

Date: 1 Oct 82      Prot No: 81/31      Status: Terminated  
Title:

Transfer of  $^{131}\text{I}$  from Male to Female During Sexual Intercourse

Start Date: April 1981      Est Comp Date: Sept 82  
Principal Investigator:      Facility:  
CPT Michael L. Smith, PhD

Dept/Sec: Dept Clinical Invest      Assoc Investigators  
Key Words:

$^{131}\text{I}$ ; Spermatogenesis

Accumulative MEDCASE      Est      Periodic  
Cost      OMA Cost:0(\$405)      Review Results  
Study Objective:

$^{131}\text{I}$  is often given to patients who have had their thyroid removed because it contained a malignant tumor. The diffusion of  $^{131}\text{I}$  to the semen of male patients and subsequent transfer to female sexual partners is not known. The purpose of this study is to determine if  $^{131}\text{I}$  given to thyroidectomized and normal male rats is concentrated in the semen and subsequently transferred to female rats during sexual intercourse. Also the effects of the  $^{131}\text{I}$  on spermatogenesis will be investigated.

Technical Approach:

Male rats will be divided into four groups.

Group 1: Five controls, no procedures.

Group 2: Five thyroidectomized rats, no procedures

Group 3: Five thyroidectomized rats, receive 1 mCi  $\text{Na}^{131}\text{I}$ .

Group 4: Five nonthyroidectomized rats, " " "

Rats will be allowed to breed and both the male and their female partners will be monitored with a single channel spectrometer for radioactive uptake and decay. The male rats will be killed after one month and rete testes fluid and testicular biopsy will be examined for abnormal sperm morphology.

Progress:

Personnel shortages precluded further work on this protocol.

Detail Summary Sheet

Date: 1 Oct 82      Prot No: 81/32      Status: Terminated

Title:

Polyamines as Chemical Markers of the Response of Patients Being Treated for Cancer

Start Date: Jan 82      Est Comp Date: Jan 84

Principal Investigator:      Facility:

CPT Michael L. Smith, PhD

Dept/Sec: Dept Clinical Invest      Assoc Investigators

Key Words:

Polyamines

Accumulative MEDCASE      Est      Periodic  
Cost      OMA Cost: \$467      Review Results

Study Objective:

Our objective is to see if serum and urinary polyamines can be used as tumor markers to follow the progress of patients being treated for cancer.

Technical Approach:

Patients with carcinoma of the colon or ovary will be used for the study. Serum and urine polyamines will be measured before, during, and after treatment. Polyamine levels and distributions will be compared to clinical signs and evaluated for clinical usefulness.

Progress:

Personnel shortages precluded further work on this protocol.



Detail Summary Sheet

Date: 1 Oct 82 Prot No: 81/33 Status: Ongoing

Title:

Study of the Size and Charge Heterogeneity of Prolactin in Human Seminal Plasma and Spermatozoa

Start Date: April 1981

Est Comp Date: Dec 1982

Principal Investigator:

Facility:

CPT Michael L. Smith, PhD

Dept/Sec: Dept Clinical Invest

Assoc Investigators

Key Words:

Prolactin; Seminal fluid; Spermatozoa

Accumulative MEDCASE  
Cost

Est

OMA Cost: \$184(716)

Periodic

Review Results

Study Objective:

Prolactin in physiological fluids exists in several forms which differ in molecular weight or molecular charge. Our objective in this study is to identify these forms of prolactin in seminal plasma and spermatozoa and to quantitate them. Identifying and quantitating these forms of prolactin may eventually lead to an understanding of their roles in semen and fertility.

Technical Approach:

Semen samples from males undergoing fertility evaluation will be collected. Those samples with high sperm counts will be saved. Three aliquots of each sample, (1) semen, (2) seminal plasma, and (3) sperm extracts, will be fractionated by sephadex chromatography and the molecular weight distribution of prolactin will be determined by radioimmunoassay of the fractions. The charge heterogeneity will be shown by isoelectric focusing and radioimmunoassay.

Progress:

Three samples were collected and prepared for processing. Research on discarded samples from the Department of Pathology was used to develop HPLC techniques. To date a size exclusion and a reversed phase technique have been developed for separating sperm extracted proteins. The RIAs for PRL and HCG have also been developed. Actual samples will be analyzed beginning in November 1982. Parts of the initial work on this project were included in a review article entitled "Prolactin in Seminal Fluid" Arch Andrology 9:105-113, 1982.

# Detail Summary Sheet

Date: 1 Oct 82      Prot No: 81/34      Status: Ongoing  
Title:

Location of Prolactin, HCG, LH, and FSH in Human Semen: An Immunocytochemical Study

Start Date: Dec 1981      Est Comp Date: Mar 1983  
Principal Investigator:      Facility:

CPT M.L. Smith, PhD

Dept/Sec: Dept Clinical Invest      Assoc Investigators  
Key Words:

Prolactin; Human Chorionic Gonadotropin; Luteinizing Hormone; Follicle-stimulating hormone; Immunocytochemistry

Accumulative MEDCASE	Est	Periodic
Cost	OMA Cost:\$1446(1446)	Review Results-

Study Objective:

The hormones prolactin, HCG, LH, and FSH have been found in semen. HCG and some prolactin is known to be associated with spermatozoa. This study proposes to determine the distribution of these hormones between oval spermatozoa, other morphological cells, and seminal plasma. This will be done by immunofluorescent techniques, light microscopy, and electronmicroscopy.

## Technical Approach:

Semen will be collected from volunteers. Sperm will be separated, washed, then subjected to Sternberger's peroxidase antiperoxidase reaction. They will be observed and photographed using light microscopy. If hormone binding is observed, the sperm will also be examined by electron microscopy. Hormone distribution will be determined from electron micrographs.

## Progress:

Antiserum for immunofluorescent studies has been purchased and some of the slide preparations have been developed under another protocol. No actual studies have been accomplished due to the work load of the Electron Microscopy Section in the Department of Pathology and the absence of an EM technician in the Microbiology Service, Department of Clinical Investigation.

# Detail Summary Sheet

Date: 1 Oct 82      Prot No: 81/46      Status: Ongoing  
Title:

Inhibition of the Uterine Vascular Effects of 17 $\beta$ -Estradiol with the H<sub>2</sub> Receptor Antagonist Cimetidine; Cortisol; an Adrenergic Blocking Agent, Phentolamine; and Cycloheximide

Start Date:      Est Comp Date:  
Principal Investigator:      Facility:

COL L.L. Penney, MC

Dept/Sec: Dept Clinical Invest      Assoc Investigators  
Key Words:

17 $\beta$  Estradiol; uterine blood flow; cimetidine; cortisol;  
phentolamine; cycloheximide

Accumulative MEDCASE	Est	Periodic
Cost	OMA Cost:\$1210(1210)	Review Results

Study Objective:

To quantify uterine blood flow responses two hours after a standard stimulating dose of 17 $\beta$  estradiol given IV to oophorectomized rabbits pretreated with one of the specified agents.

## Technical Approach:

The experimental model used in our previous work, Protocol 78/26, and in a current submission for publication, "17 $\beta$ -Estradiol Stimulation of Uterine Blood Flow in Oophorectomized Rabbits with Complete Inhibition of Uterine RNA Synthesis" will be used to determine uterine blood flow with microspheres at time zero and two hours after estradiol, 10 ug/kg IV, in animals pre-treated with cimetidine 10 mg/kg; cortisol 20 mg/kg; phentolamine 10 mg/kg or cycloheximide 4 mg/kg. Twelve animals will be studied in each group and every animal will serve as its own control for comparison by paired t-test within groups.

## Progress:

Ten rabbits each in the cycloheximide, cortisol and cimetidine groups have been studied. Additional animals in the cortisol group will need to be studied because of extremely variable results. The phentolamine group will also be completed in FY83.

Detail Summary Sheet

Date: 1 Oct 82      Prot No: 81/47      Status: Ongoing  
Title:

Variability of Estradiol Induced Increases in Uterine Blood Flow as  
a Function of Time Post-oophorectomy

Start Date:      Est Comp Date:  
Principal Investigator:      Facility:

COL L.L. Penney, MC

Dept/Sec: Dept Clinical Invest      Assoc Investigators  
Key Words:

17B estradiol; uterine blood flow

Accumulative MEDCASE      Est      Periodic  
Cost      OMA Cost:\$650(650)      Review Results  
Study Objective:

To establish the lack of responsiveness of uterine blood flow to  
estradiol stimulation in rabbits oophorectomized longer than 60 days.

Technical Approach:

We have recently completed a study of the effects of Actinomycin D  
on estradiol-induced increases of uterine blood flow in  
oophorectomized rabbits. During that experiment, a delay in  
shipping labeled microspheres necessitated study of a small group of  
control animals 60 days post-operatively as opposed to between 1-5  
weeks as had been the case. At 60 days an increase in uterine blood  
flow 2 hours following estradiol, 10 ug/kg, was no longer  
demonstrable. Such a change with time has not previously been  
reported. We wish to repeat the study with sufficient numbers of  
animals to confirm or refute this observation.

Progress:

The observation has been extended to ten animals in the 60-70 days  
post-oophorectomy time frame and appears to hold. Further animals  
in the 40-60 day range need to be studied to determine the  
transition point.

Detail Summary Sheet

Date: 1 Oct 82      Prot No: 81/48      Status: Ongoing  
Title:

Variability in Quantifiable Uterine Cytosolic and Nuclear Estrogen Receptors as a Function of Time Following Oophorectomy in Rabbits.

Start Date:      Est Comp Date:  
Principal Investigator:      Facility:

COL L.L. Penney, MC

Dept/Sec: Dept Clinical Invest      Assoc Investigators  
Key Words:

17 $\beta$  estradiol; estrogen receptors

Accumulative MEDCASE      Est      Periodic  
Cost      OMA Cost: 0(\$618)      Review Results  
Study Objective:

To correlate the amount of receptor present with the degree of blood flow response to 17 $\beta$  estradiol.

Technical Approach:

If protocol 81/47 confirms a diminished response of uterine blood flow to 17 $\beta$  estradiol, as a function of time following operation, this study will be conducted. Since a decreased response is in a sense natural inhibition a quantification for the receptors should aid in elucidating the basic mechanism. In addition to the cytosolic receptor, eosinophilic and  $\alpha$ -adrenergic receptors, as well as any others suggested by Protocol 81/46 will be examined by standard techniques detailed in the references. For each receptor 6-8 animals will be studied at 20-40 days following operation and another 6-8 at 60-80 days.

Progress:

Preliminary work on methodology has been started. Further work is pending and will parallel Protocol 81/47 - that is the times to be studied will depend on the results of Protocol 81/47.

Detail Summary Sheet

Date: 1 Oct 82 Prot No: 81/53 Status: Terminated  
Title:

Prostacyclin Synthetic Capability of Thoraco-Abdominal Aortic Dacron  
Graft One Year Post-Surgery

Start Date: Est Comp Date:  
Principal Investigator: Facility:

D.O. Rauls, PhD, DAC

Dept/Sec: Dept Clinical Invest Assoc Investigators  
Key Words:

Prostacyclin; aortic grafts; neointima

Accumulative MEDCASE Est Periodic  
Cost OMA Cost:\$200(200) Review Results  
Study Objective:

The objective of this study is to determine whether or not the  
neointima formed along the interior of Dacron aortic grafts develops  
the capability of producing prostacyclin.

Technical Approach:

Animals with Dacron aortic grafts are available from another  
protocol. The animals will be sacrificed and a portion of the graft  
will be removed and incubated with <sup>14</sup>C-arachidonate. The  
prostacyclin metabolite 6-oxo-prostaglandin F<sub>2</sub> will be determined  
by thin layer chromatography.

Progress:

Personnel shortages precluded further work on this protocol.

# Detail Summary Sheet

Date: 1 Oct 82	Prot No: 82/08	Status: Completed
Title: Mitogenic Potential of Medicago Sativa (Alfalfa) Seeds		
Start Date:	Est Comp Date:	
Principal Investigator: CPT Charles S. Serio, PhD	Facility:	
Dept/Sec:	Assoc Investigators	
Key Words: Immune function; alfalfa		
Accumulative MEDCASE Cost	Est OMA Cost:	Periodic Review Results
Study Objective:		

The primary objective is to examine the mitogenic activity of Medicago sativa extracts (sprouts and seeds) and their potential as an immunological tool for the activation of lymphocyte populations. The eventual goal is the evaluation of changes in cellular immune functions during such clinically significant events as malignancies, infections, or allergic reactions.

## Technical Approach:

The primary objective of this protocol has been achieved by determining a number of biological activities that are associated with crude extracts of alfalfa seeds and sprouts to include antibacterial, mitogenic and hemagglutinating activities. We are now concentrating our efforts onto identifying and separating the various alfalfa components responsible for the above named activities.

## Progress:

Organic and phosphate buffered saline extracts from seeds and sprouts of Medicago sativa (alfalfa) demonstrate antibacterial, hemagglutinating, and possible mitogenic activity. The antibacterial activity against gram (+) and gram (-) bacteria was demonstrated with the crude ether, chloroform, and ethyl acetate precipitates of alfalfa sprouts in milligram quantities. These sprout extracts agglutinate human, sheep, dog, rat, and rabbit erythrocytes. In stimulation assays utilizing  $2 \times 10^5$  human peripheral blood lymphocytes (PBL) per microtiter well, both seeds and sprout extracts were dose sensitive, and when compared with the known mitogens, phytohemagglutinin and concanavalin A, were equally, if not more, sensitive in their ability to stimulate PBLs. These results suggest a possible new immunological tool for the activation and/or regulation of lymphocyte populations.

# Detail Summary Sheet

Date: 1 Oct 82 Prot No: 82/14 Status: Ongoing

Title:

Serum and Urinary Electrolyte and Steroid Concentrations During Danazol Administration

Start Date:

Est Comp Date:

Principal Investigator:

Facility:

COL L.L. Penney, MC

Dept/Sec:

Assoc Investigators

Key Words:

Danazol; Electrolyte; Steroid

Accumulative MEDCASE

Est

Periodic

Cost

OMA Cost:\$657(647) Review Results

Study Objective:

To further define electrolyte changes occurring during danazol administration and to examine indirectly potential sites of inhibition in the metabolic pathways involved.

Technical Approach:

Standard methods of testing the mineralocorticoid pathway are available. The effects of danazol will be tested on days 6 and 12 to coincide with references in which testing was done on day 6. Our observation has been significant cramps and edema are noted 10 days to 2 weeks after starting therapy. Patients will receive 200 mg of danazol four times a day. Only those patients with documented endometriosis who will be treated as part of this therapy with danazol will be asked to participate. In addition to the battery of tests outlined in the flow chart (see below) patients will be asked to submit a serum sample at 8 a.m. for deoxycorticosterone (DOC), aldosterone (A), plasma renin activity (PRA), Na and K and to collect a 24-hour urine specimen on days 3 and 9. Aliquots of serum will be kept frozen for possible analyses of 18-hydroxycorticosterone (18OHB), corticosterone (B) or other steroids. Na, K, and possibly aldosterone will be determined on each urine collection and aliquots will be frozen for subsequent analyses (by GC-MS) as might be suggested by the serum results. Results will be collated and data analyzed by appropriate t-test after 5-6 patients have been entered to determine the need and direction of further testing.



Study Plan and Flow Chart:

- Day (-10): Subjects begin 120 mEq Na and 80 mEqK diets after 24 hour urine Na and K (Day 1 of menstrual cycle).
- Day (-5): 24-hour urine Na and K
- Day (0) : A) 24-hour urine Na and K completed by 0700
- B) Baseline serum Ca, P, K, DOC, B, 18-OHB, A, PROG, 17OHP, F, DHEA and PRA.
- C) Infusion of 25 units (0.25 mg) of ACTH intravenously at 0900. Patient supine from 0700 until 1030.
- D) Serum drawn at 0930, 1000 and 1030 from arm opposite the infusion. All serum to be frozen and baseline and 1000 samples to be analyzed; otherwise samples to be studied if needed. Patient starts danazol. at conclusion of sampling.
- Day (6): Repeat Day (0). Patient on danazol.
- Day (12): Repeat Day (0). Patient on danazol.

Progress:

Three patients have completed the protocol. The PRA and urinary and serum electrolytes have been analyzed, but the remaining specimens are frozen. When five patients have been entered all specimens will be run.

# Detail Summary Sheet

Date: 1 Oct 82	Prot No: 82/32	Status: Ongoing
Title: Effect of Verapamil on Gestational Length in Rabbits		
Start Date:	Est Comp Date:	
Principal Investigator: COL L.L. Penney, MC	Facility:	
Dept/Sec: Dept Clin Investigation	Assoc Investigators	
Key Words: Verapamil; Gestation		
Accumulative MEDCASE Cost	Est OMA Cost:\$1440(1440)	Periodic Review Results
Study Objective:		

This is the second in a series of projects designed as preliminary studies to evaluate the potential value of verapamil as a tocolytic agent in the prevention of premature labor.

## Technical Approach:

Pregnant rabbits whose time of conception is known within two hours will be used. The rabbits will be randomly divided into two groups and one group will receive oral verapamil in three equally spaced doses beginning on the 22nd day of gestation. The length of gestation will be recorded in all animals. Observations will be made regarding their respiratory status and survival of the pups. The control group will receive placebo in place of verapamil. A second cohort of rabbits will be similarly treated, but will also receive subcutaneous oxytocin 0.5 units every day at 0800, beginning on the 24th day of gestation.

## Progress:

Thirty-six rabbits divided into seven groups have been studied. Gestational length in five control animals was  $32 \pm 0.4$  (X  $\pm$  SEM) days. There was no significant change in gestational length with 0, 20 or 40 mg/kg of verapamil given orally from day 25. Oxytocin decreased mean gestational length 2 days. This was unchanged by verapamil 10 mg/kg, but returned to normal with 20 mg/kg orally. These results will be confirmed with subcutaneous administration.

# Detail Summary Sheet

Date: 1 Oct 82 Prot No: 82/33 Status: Ongoing  
Title:

In Vitro Effects of Spironolactone on Gonadotropin Production by the Rat Pituitary and Androgen Formation by the Rat Ovary

Start Date: Est Comp Date:  
Principal Investigator: Facility:

COL L.L. Penney, MC

Dept/Sec: Dept Clin Investigation Assoc Investigators  
Key Words:  
Spironolactone; Hormones

Accumulative MEDCASE	Est	Periodic
Cost	OMA Cost:\$90(90)	Review Results
Study Objective:		

This project is designed as a preliminary study to determine if spironolactone, acting either primarily or secondarily, inhibits gonadotropin production from the pituitary in this animal model.

## Technical Approach:

Estrous rats will be sacrificed and the anterior pituitary removed for culture by established techniques. Similarly, the ovaries will be removed and separated into granulosa cell and remaining theca and stroma as published. FSH and LH will be determined by radioimmunoassay with reagents obtained from the NIH. The gonadotropins will be measured in the media of the cultured pituitary glands as a baseline and with spironolactone in concentrations of 0.15, 1.0, and 2.0 X 10<sup>-6</sup>M respectively. Glands will also be cultured in physiological concentrations of testosterone, estradiol, and estrone. Once these control levels of gonadotropin release into the media are determined, the experiment will be repeated with spironolactone combined with testosterone, estradiol and estrone individually. The effects of these same concentrations of spironolactone will also be determined on basal and gonadotropin stimulated sex steroid production from the cultured granulosa cells and ovarian stroma.

## Progress:

Tissue culture techniques are being perfected. The actual study should commence by mid-FY83.

Detail Summary Sheet

Date: 1 Oct 82      Prot No: 82/39      Status: Ongoing

Title:

Histamine Concentration in Follicular Fluid: Correlation with  
Follicular Size and Maturation in the Perioovulatory Period

Start Date:      Est Comp Date:  
Principal Investigator:      Facility:

COL L.L. Penney, MC

Dept/Sec: Dept Clin Investigation      Assoc Investigators  
Key Words:

Histamine; Follicular fluid

Accumulative MEDCASE      Est      Periodic  
Cost      OMA Cost:      Review Results

Study Objective:

To obtain preliminary data regarding a possible role of endogenous  
histamine in ovulation.

Technical Approach:

Mature, virgin New Zealand white rabbits will be used. Follicular  
size will be recorded and follicular fluid histamine content  
measured prior to a standard IM dose of HCG and 2,4,8,12 and 16  
hours following HCG in separate groups of animals. Serum estradiol  
and progesterone will be measured at the time of ovarian sampling in  
all animals.

Progress:

Work has not begun on this protocol approved late in FY82.

# Detail Summary Sheet

Date: 1 Oct 82 Prot No: 82/48 Status: Ongoing  
Title:

Potentiating Effect of B-Adrenergic Agents on Rat Spleen Cells and Peripheral Blood Lymphocytes in vivo

Start Date: Est Comp Date:  
Principal Investigator: Facility:  
R.J. Frederick, PhD,DAC

Dept/Sec: Assoc Investigators  
Key Words:

Terbutaline; Lymphocytes

Accumulative MEDCASE Est Periodic  
Cost OMA Cost: \$130(130) Review Results  
Study Objective:

The objective is to provide experimental evidence that B-adrenergic agents have a direct effect on cells involved in immunological processes.

## Technical Approach:

Sprague-Dawley white rats will be used as a model for our experiments. We will first establish a dose response effect by varying the concentration of terbutaline administered and assaying by an in vitro blast transformation assay using H<sup>3</sup>-thymidine incorporation as a measure of DNA synthesis. Secondly, the time course of the potentiated state will be monitored by injecting a group of rats with the "optimum" dose of terbutaline and taking sequential blood samples over a course of three weeks. Rats given a saline bolus instead of the drug will be used as controls. All in vitro assays will be done using PHA, Con A, and the B-cell specific mitogens Salmonella lipopolysaccharide and protein A. Where appropriate, spleen and thymus cells will also be assayed for response to mitogenic stimulation. Small portions of the sera collected will be reserved for immunoglobulin determinations.

Cells from treated rats will be tested for drug enhanced stimulation of antigen induced DNA synthesis in vitro.

# Progress:

The beta agonist terbutaline was studied for its role as a possible biological response modifier. The modulation of thymic (TL), peripheral blood (PBL), and splenic lymphocytes (SL) by terbutaline were measured using the in vitro blast transformation assay in response to phytohemagglutinin (PHA) and concanavalin A (ConA). the i.p. injection of a single dose of terbutaline sulfate into 16 Sprague-Dawley rats produced significant long-term effects in SL and to a lesser degree PBL, but not TL. The response of SL was dose and time dependent with maximum values being achieved between 10 to 300 ug terbutaline per kg at 7 days post-injection with reduced activity at 14 days. Responses (mean  $\pm$  SEM) to 8 ug of ConA per  $2 \times 10^5$  SL were as follows:

	7 days	14 days
A-1 mg/kg	213,720 $\pm$ 1984	86,030 $\pm$ 561
B-300 ug/kg	246,775 $\pm$ 3500	81,867 $\pm$ 8600
C-10 ug/kg	219,340 $\pm$ 2700	50,855 $\pm$ 2300
D-Controls	162,200 $\pm$ 10,000	47,671 $\pm$ 313

This study suggests long-term enhancement of specific lymphocyte populations in response to a single injection of terbutaline. Our observed positive effects by terbutaline on the immune system were not shown with in vitro incubation by others with isoproterenol. These observed differences may well be dependent on in vivo activation by terbutaline followed by in vitro mitogen stimulation compared to in vitro activation and stimulations by isoproterenol and specific mitogens.

Abstracts of our data will be presented at the American Academy of Allergy and Immunology meeting in Hollywood, Fla, and at the Carl W. Temple Symposium on Allergy at Fitzsimons Army Medical Center, Aurora, CO.

# Detail Summary Sheet

Date: 1 Oct 82	Prot No: 82/57	Status: Ongoing
Title: Cardiovascular Effects of Delta-9-Tetrahydrocannabinol in the Pregnant Conscious Sheep		
Start Date:	Est Comp Date:	
Principal Investigator: COL L.L. Penney, MC	Facility:	
Dept/Sec: Dept Clin Investigation	Assoc Investigators	
Key Words: Delta-9-THC; Cardiovascular effects		
Accumulative MEDCASE Cost	Est OMA Cost:	Periodic Review Results
Study Objective:		

To delineate the effects of intravenous delta-9-THC on cardiovascular and acid base parameters in the conscious pregnant sheep comparing variable doses and rates of administration.

## Technical Approach:

Twelve pregnant sheep at approximately 135 days' gestation will be studied. An indwelling Swan-Ganz catheter and a carotid arterial catheter will be placed under pentobarbital anesthesia. These catheters will be maintained open with a heparin lock and the sheep will be given antibiotics. Utilizing a paired t-test and randomized block (or appropriate variance as per consultation with statistician) design the sheep will be treated 24 hours postoperatively with either 0.25 mg/kg, 0.5 mg/kg, or 1 mg/kg of delta-9-THC injected in the pulmonary artery. Baseline recordings will be obtained prior to injection and cardiac output will be monitored at 3, 5, 15 and 60 minutes and at hourly intervals thereafter until recovery occurs. CVP will also be monitored at the same times. Continuous monitoring of the heart rate and blood pressure will be conducted and blood gases will be drawn at 5, 15, and 60 minutes and thereafter until recovery has occurred. Following rest periods of 48 hours, each sheep will be studied at the next dose in its scheme until all sheep have been studied with each of the three doses. Forty-eight hours after the final study, a continuous infusion of 10 ug/kg/min for three hours will be conducted and monitoring continued at hourly intervals until recovery occurs. The sheep will be salvaged, if possible. Serum samples will be saved at each blood gas sampling for possible analysis of THC concentration

## Progress:

This protocol is programmed for Jan-Feb 83.

Detail Summary Sheet

Date: 1 Oct 82      Prot No: 82/59      Status: Ongoing

Title:

Restriction Enzyme Analyses of E. Coli Bacterial Chromosomes and Their Membrane-Associated Sequence

Start Date: 1 Feb 83

Est Comp Date:

Principal Investigator:

Facility:

R.J. Frederick, PhD, DAC

Dept/Sec:

Assoc Investigators

Key Words:

DNA; Membrane bound sequences

Accumulative MEDCASE

Est

Periodic

Cost

OMA Cost:

Review Results

Study Objective:

The objective will be to analyze membrane associated chromosomal DNA sequences to determine specificity and possible function as a regulatory mechanism in bacterial growth.

Technical Approach:

Bacterial nucleoid isolation and the determination of membrane bound DNA fragments will be done as described previously. A refined quantitation scheme incorporating an improved method for agarose gel electrophoretic analysis of restriction enzyme fragments will be used to estimate the average size of membrane associated DNA. We can then calculate the average number of inherent membrane attachment sites on the bacterial chromosome. These estimates will be compared with results obtained using different restriction enzymes and the techniques reported in the literature. Comparable numbers will add validity to the technique since these should not vary significantly from enzyme to enzyme despite very different average segment size.

Isolated membrane associated DNA fragments will be analyzed to determine if they are a unique subset of the entire chromosome by performing rehybridization kinetics and second restriction enzyme analyses. If successful, pulse labeling experiments will be done using E coli mutant strains with temperature sensitive replication mechanisms. Comparative studies of specific DNA fragments can then be done by hybridization assays using labeled probe from temperate phage carrying known sequences of the bacterial DNA.

Progress:

Approved late FY82 and not initiated as of review date.



# Detail Summary Sheet

Date: 1 Oct 82 Prot No: 82/61 Status: Ongoing

## Title:

Use of Flow Cytometry to Isolate Novel Revertants of E. coli  
Partition Deficient Mutants

Start Date:

Est Comp Date:

Principal Investigator:

Facility:

R.J. Frederick, PhD, DAC

Dept/Sec: Dept Clin Investigation

Assoc Investigators

## Key Words:

Flow cytometry; Bacterial mutant enrichment

Accumulative MEDCASE  
Cost

Est  
OMA Cost:

Periodic  
Review Results

## Study Objective:

This study is planned to evaluate the use of flow cytometry as an enrichment process in procedures for the isolation of bacterial mutants.

## Technical Approach:

Escherichia coli DNA partition (PAR) mutants will be used for the initial screening procedures. At temperatures over 40°C, these mutants stop cell division but continue to replicate their DNA resulting in enlarged cells with four to eight genome equivalents of DNA. The first objective will be to establish that the mutant phenotype can be distinguished from wild type cells in the Ortho Cytofluorograph. Cultures will be given at 41°C and 30°C, diluted and mixed with media containing ethidium bromide (DNA stain). The mixed culture will be sorted on the basis of cell size and quantity of DNA (fluorescence intensity) per cell. The efficiency of sorting will be evaluated by microscopic examination under phase and fluorescence illumination. Once the separation conditions are determined revertants may be selected on the basis of their wild type phenotype when grown at 41°C. After sorting, single colony isolates will be screened for temperature sensitivity, i.e., ability to multiply at 41°C. Intragenic or suppressed revertants should grow while extragenic or second site revertants may or may not. Those that did not have the PAR phenotype, but could not grow at 41°C would be the strains of interest initially. Such novel revertants would establish the feasibility of the technique and possibly lead to further insight on the problem of the regulation of bacterial growth.

## Progress:

Approved late FY82 and not initiated as of review date. Starting date is contingent upon installation of flow cytometer.

# Detail Summary Sheet

Date: 1 Oct 82	Prot No: 82/62	Status: Ongoing
Title: Analyses of Copper Complexes in Plasma		
Start Date:	Est Comp Date:	
Principal Investigator: David Rauls, PhD, DAC	Facility:	
Dept/Sec: Dept Clin Investigation	Assoc Investigators	
Key Words: Copper salicylates		
Accumulative MEDCASE Cost	Est OMA Cost:	Periodic Review Results
Study Objective:		

To develop methodology for the analysis of copper salicylate complexes in plasma and measure blood levels attained upon administration of these complexes to rats.

## Technical Approach:

Copper diisopropyl salicylate will be prepared by literature methods. Optimum conditions for analysis of the complex by high performance liquid chromatography will be worked out on the pure substance followed by isolation of the complex from spiked plasma to determine recovery and interferences. Attempts will be made to utilize atomic absorption spectroscopy for quantification of the complex in order to obtain adequate sensitivity. Once the accuracy, precision, and sensitivity of the assay have been established, the copper diisopropyl salicylate will be injected into rats intraperitoneally at doses (100 mg/kg) found to inhibit maximal electroshock seizures in rats. Blood samples will be analyzed at 0.5, 2, and 4 hours post-injection. The existence of the intact copper complex in plasma will be considered proven if a copper containing peak is recovered from injected rat plasma having a HPLC retention time equivalent to that of the pure copper diisopropyl salicylate and such a peak is found to be absent from a plasma sample from a rat injected with vehicle only.

## Progress:

Approved late FY82 and not initiated as of review date.

# Detail Summary Sheet

Date: 1 Oct 82      Prot No: 81/25      Status: Completed  
Title:

A Clinical Comparison of Antibiotic Steroid Preparations Used in  
Post Extraction Mandibular Third Molar Sites to Reduce Associated  
Post-Operative Sequellae

Start Date:      Est Comp Date:  
Principal Investigator:      Facility:

LTC J.R. Zwolensky, DC

Dept/Sec: Dept Dentistry      Assoc Investigators  
Key Words:

Molar extractions; glucocorticoids; antimicrobial agents; alveolitis

Accumulative MEDCASE      Est      Periodic  
Cost      OMA Cost:      Review Results

Study Objective:

To conduct a prospective randomized, single-blind comparison of  
three different antibiotic-steroid regimens used immediately  
post-operatively in patients undergoing impacted third molar surgery  
and their efficacy in reducing post-operative pain, trismus and  
localized alveolitis.

Technical Approach:

A total of 160 patients with bilateral impacted third molars will be  
divided into four groups of 40 patients each. Patients eligible for  
inclusion must be adults 18 years of age or older. Males may be  
military active duty or military dependent. If this study proves  
significant other groups may be evaluated in the future. Patients  
to be excluded from this investigation are those who give a history  
of systemic disease, prior steroid therapy or are taking oral  
contraceptives at time of surgery. Catellani, Harvey, Erickson and  
Cherkin have shown a significant increase of incidence of localized  
alveolitis (dry socket) over the general population in patients  
taking contraceptives at the time of third molar surgery. Schow  
reported an incidence of 45% localized alveolitis in patients taking  
oral contraceptives as opposed to that in the general population.

Progress:

When compared with the control group in terms of postoperative pain  
and trismus, the petrolatum group showed the best results with an  
average of 7.9 pills needed over a period of 2.4 days and at one

week postop, an aggregate average interincisal opening of 94.1% of preoperative measurements. The eucerin group showed the second best results, needing an average of 8.8 pills over 1.8 days and at one week postop, the average interincisal opening of 92.8% of the preoperative measurements. The mineral oil group obtained the least desirable results of the three vehicle groups needing 9.2 pills over 2.6 days and at one week postop, an interincisal opening of 90.1% of the preoperative measurements. The control group needed an average of 13.3 pills over 3.9 days and at one week postop the average interincisal opening was 82.8% of the preop measurements. Biopsies performed on one subject from each group showed no evidence of Lipogranuloma formation (Myospherulosis). Although eight patients were lost to followup, of the forty subjects followed for the full three months, none showed evidence of localized alveolitis by visual inspection of the surgical sites, intractable pain not obtunded by oral analgesics or the need for a local obtundant dressing.

In summary, although the best results clinically were obtained using the steroid-antibiotic preparation in the petrolatum vehicle, all three vehicles showed that fewer number of pills were needed for a shorter period of time and that the subjects in all three vehicle groups at one week postop experienced less trismus when compared with the control group. While maintaining good surgical technique, steroid-antibiotic preparations appear to be helpful in reduction of postoperative sequelae of surgical dental extractions.

Detail Summary Sheet

Date: 1 Oct 82      Prot No: 81/26      Status: Completed  
Title:

Use of Op Site Transparent and Permeable Adhesive Dressing in Skin Grafting

Start Date:      Est Comp Date:  
Principal Investigator:      Facility:

LTC D.P. Gluhm, DC

Dept/Sec: Dept Dentistry      Assoc Investigators  
Key Words:

Skin grafts

Accumulative MEDCASE      Est      Periodic  
Cost      OMA Cost:      Review Results

Study Objective:

Evaluate a commercially available sterile dressing OpSite for use as a wound dressing, a barrier to infection, a vehicle for handling donor graft tissue, and its effects upon patient comfort, patient recovery time, and patient acceptance.

Technical Approach:

Patients to be included must be at least 18 years of age, military or dependents, active duty or retired, of either sex. Patients will be excluded if they give a history of previous skin graft and request a specific donor site dressing previously employed. All patients will undergo a ten minute Betadine surgical prep to the proposed graft harvest site, following standard razor prep of the area the day of surgery. All harvest sites will be defatted with acetone prior to harvest. All harvest sites will be covered with OpSite dressing prior to harvest. All split thickness and full thickness grafts will be harvested through the OpSite dressing. All residual OpSite will be removed and the area again defatted. All harvest sites will be treated with the application of a 1/100,000 epinephrine solution prior to application of OpSite dressing.

Followup will consist of routine post-op care, to include observation for signs of infection. Postoperative infection will be treated with local measures based upon culture and sensitivity. All infections will be cultured utilizing aerobic and anaerobic methods. Excess fluid accumulating beneath the OpSite dressing will be drained for C and S to prevent spontaneous leaking or rupture, following 10 minute Betadine prep. Dressing will be removed by the patients themselves while bathing on the 10th postoperative day.

Patients may shower at will following surgery, but will be instructed not to scrub the dressing. Patients will be allowed and encouraged to ambulate at will following surgery. Patients will be requested to complete a questionnaire at one week and one month following surgery.

Progress: Our study consisted of twenty adult edentulous patients, average 44.95 years, chosen because of the amount of mandibular atrophy displayed. Each patient was scheduled for a STSG to the mandible with or without a lowering of the floor of their mouth. Two patients also underwent maxillary procedures to improve the available maxillary ridge. The patients were informed as to the proposed procedures and asked if they were interested in participating in a study of a new technique utilizing a new type of dressing. Each prospective patient was informed that, at a later date, each would be asked to complete a questionnaire covering their awareness of the dressing and asking their opinion as to their satisfaction. A nineteen item questionnaire was then administered at approximately ten days and 30 days post-surgery to ascertain their feelings at the time of dressing removal and at one month post surgery.

Patient reaction was overwhelmingly in favor of the new technique. This was felt to be due in part to their interaction with other patients on the ward who had experienced other types of postoperative care and dressings. Hospital stay was decreased, discomfort ranged from minimal to unaware, postop care was minimal, as was the wound care required by the patient and the ward staff. Without exception all patients were pleased to have full showering privileges postop without the fear of damaging bulky dressings. Post-anesthetic problems were similarly decreased because, following the recovery phase, all patients were allowed to ambulate freely, thus decreasing atelectasis and fever. No incidents of thrombophlebitis or phlebothrombosis were recorded. Nursing care was greatly decreased because no dressing changes were required and no bed baths were needed. Actual nursing time was spent with routine vital signs, dressing checks and passing indicated medications. Routine requests for pain medication were, in fact, all directed toward amelioration of intraoral discomfort, specifically that associated with the passing of mandibular awls.

Mastery of this technique is straight forward and almost free of troublesome complications encountered in most reports of new surgical procedures. The graft is harvested through a portion of the new dressing by routine harvest techniques. A factor of 0.002" is needed to compensate for the thickness of the Op-Site dressing in addition to the desired thickness of the graft to be harvested. The vestibuloplasty and graft application procedure is followed much the same as that classically described by MacIntosh and Obwegeser.

Meshing of the graft is not indicated; first, because of the relatively small size of the graft needed and, second, because if used with the Op-Site semi-permeable technique, with the buildup of tissue fluid the meshed graft will float up from the harvest surface and actually cause an interference with re-epithelialization.

Postoperative evaluation of patients after one year shows minimal change in their attitude toward their experience. Satisfaction with the dressing remained high. Evaluation of the donor sites at up to a year postop revealed excellent tissue coloration and texture. Tissue surface character was of similar local nature. Tissue sensitivity was excellent.

Overall advantages noted:

Freedom from postoperative pain. A barrier to bacterial invasion. Early re-epithelialization of harvest site. Ease of handling graft for placement in the splint. Ease of application and removal. Low amount of postop care needed. Easy visibility of healing due to its transparency. Lack of bulky dressing. Early bathing privileges. Rapid ambulation.

Possible disadvantages include the chance of postoperative fluid leak with risk of bacterial invasion.

# Detail Summary Sheet

Date: 1 Oct 82	Prot No: 82/19	Status: Ongoing
Title: Evaluation of the Mandibular Staple Bone Plate and the Ramus Frame Implant in the Rehabilitation of the Atrophic Edentulous Mandible.		
Start Date:	Est Comp Date:	
Principal Investigator: COL F.C. Theisen, DC	Facility:	
Dept/Sec:	Assoc Investigators	
Key Words: Mandibular rehabilitation		
Accumulative MEDCASE Cost	Est OMA Cost:	Periodic Review Results
Study Objective:		

To evaluate the efficacy of two alloplastic implants in the rehabilitation of the edentulous atrophic mandible. Future application will be evaluated for the reconstruction of avulsive traumatic injuries to the mandible and ablative surgical procedures in treatment of pathology in the mandible. Factors to be evaluated include a) the surgical procedure for insertion, b) stability and retention afforded the denture, c) patient function and comfort, d) complications, e) long term followup stability and overall versatility of both implants.

## Technical Approach:

All patients selected will be approved by both the Prosthodontic Service and the Oral Surgery Service, WBAMC. Active duty personnel must have a minimum of 12 months remaining prior to anticipated ETS or PCS. Dependents or retired personnel must be residents of the El Paso area and agree to a minimum of two years followup. The patient will have a minimum of 7mm vertical osseous height for the ramus frame and 9mm for the mandibular staple as measured on a lateral cephalometric radiograph. The oral soft and hard tissues will be free of active disease of pathology. The ramus frame implant will be primarily utilized for those patients who are medically contraindicated for general anesthetic. Patients who are candidates for the mandibular staple will have all pre-implant surgical preparation done a minimum of three months prior to placement of the implant. These include alveoloplasty and vestibuloplasty with skin grafting for lowering of mucosal and muscle attachments. Medical assessment of the patient will be accomplished by the Oral Surgery Svc or by WBAMC medical staff when indicated.



The patient will be counselled on the investigational nature of the procedure, to include expected results and possible complications. The patient will be required to sign an agreement concerning his participation in the study and the required followup.

Patients will complete post-operative questionnaires during the six month postop followup visit.

#### PROGRESS

Patient accrual is commencing on this newly activated protocol.

Detail Summary Sheet

Date: 1 Oct 82      Prot No: 76/33      Status: Ongoing  
Title:

Diagnostic Adrenal Scanning with  $^{131}\text{I}$  (NP59)

Start Date:      Est Comp Date:  
Principal Investigator:      Facility:

LTC T. Brown, MC

Dept/Sec: Nuclear Medicine Svc      Assoc Investigators  
Key Words:

Adrenal scanning

Accumulative MEDCASE	Est	Periodic
Cost	OMA Cost:	Review Results

Study Objective:

The purpose of this study is to determine the usefulness of  $^{131}\text{I}$  NP59 in scanning of the adrenal glands. It will be employed for the following purposes: (a) as a screening test for detection of primary aldosterone tumor, Cushing's disease, adrenal cortical adenoma, or pheochromocytoma, (b) imaging of adrenals in patients who require adrenal venography and are allergic to contrast media, (c) detection of unilateral adrenocortical hypofunction: calcification, metastatic carcinoma, post-venography infarction, etc., (d) detection of functioning adrenal remnant after adrenalectomy for Cushing's syndrome, (e) aid in assessment of adrenocortical steroid therapy.

Technical Approach:

Patients with clinical evidence of adrenal disease will be studied upon referral from the Endocrine Service. Adrenal imaging will be performed after injection of the material to assess the presence or absence of visualization of the adrenal glands, their size and response to suppression therapy.

Progress: The annual review of this protocol was conducted 16 Sep 82. A single patient was entered on this protocol in FY82. No adverse effects were noted and an appropriately executed consent form is on file in the protocol jacket.

Detail Summary Sheet

Date: 1 Oct 82 Prot No: 79/28 Status: Terminated

Title:

SWOG 7713: Chemotherapy in Non-Hodgkins Lymphoma CHOP vs CHOP + Levamisole vs CHOP + Levamisole + BCG for Remission Induction Therapy

Start Date: Est Comp Date:

Principal Investigator: Facility:

LTC P.C. Farley, MC

Dept/Sec: Oncology Svc Assoc Investigators

Key Words:

Lymphoma

Accumulative MEDCASE Est Periodic  
Cost OMA Cost: Review Results

Study Objective:

To compare the effectiveness, in terms of rate of response two chemo-immunotherapy regimens (CHOP + Levamisole vs CHOP Levamisole BCG) against CHOP for remission induction in previous untreated patients with non-Hodgkin's lymphoma.

For patients proven to be in complete remission after induction, to compare the duration of documented complete response obtained by continued maintenance immunotherapy with Levamisole vs no maintenance therapy.

For patients with impaired cardiac function (not eligible for treatment with Adriamycin), with mycosis fungoides, or with only a partial response to 11 courses of treatment with CHOP-Levamisole-BCG, to estimate the complete response obtained by continued chemoimmunotherapy with CHOP - Levamisole.

To estimate the CNS relapse rate in patients with diffuse lymphomas when CNS prophylaxis with intrathecal cytosine arabinoside is used.

To continue to evaluate the impact of systematic restaging of patients judged to be in complete remission and the value of expert hematopathology review of diagnostic material from all cases.

To establish baseline and serial data on immunologic statute in both chemoimmunotherapy groups.

**Technical Approach:**

The details are lengthy and specified in the original SWOG protocol. Duplicates are kept on file in the Clinical Investigation Department, WBAMC, and are available upon request.

**Progress:**

See Unit Summary.

# Detail Summary Sheet

Date: 1 Oct 82	Prot No: 79/34	Status: Terminated
Title:		

SWOG 7804: Adjuvant Chemotherapy with 5-FU. Adriamycin and Metomycin C (FAM) vs Surgery Alone for Patients with Locally Advanced Gastric Adenocarcinoma Phase III

Start Date:	Est Comp Date:
Principal Investigator:	Facility:

LTC P.C. Farley, MC

Dept/Sec: Oncology Svc	Assoc Investigators
Key Words:	

Carcinoma, gastric

Accumulative MEDCASE	Est	Periodic
Cost	OMA Cost:	Review Results
Study Objective:		

To determine the efficacy of adjuvant chemotherapy with 5-Fluorouracil, Adriamycin and Mitomycin-C (FAM) on the disease-free interval and survival of patients with TNM stage-groups IB, IC, II and III gastric adenocarcinoma compared to potentially curative surgery alone.

## Technical Approach:

The details are lengthy and specified in the original SWOG protocol. Duplicates are kept on file in the Clinical Investigation Department, WBAMC, and are available upon request.

## Progress:

See Unit Summary.

Detail Summary Sheet

Date: 1 Oct 82      Prot No: 79/35      Status: Terminated

Title:

SWOG 7811: Brain Metastases Phase III

Start Date:

Est Comp Date:

Principal Investigator:

Facility:

LTC P.C. Farley, MC

Dept/Sec: Dept Medicine, Oncology

Assoc Investigators

Key Words:

Accumulative MEDCASE  
Cost

Est  
OMA Cost:

Periodic  
Review Results

Study Objective:

To determine the effectiveness of combined radiation therapy and metronidazole (Flagyl) in the treatment of patients with brain metastases from primary malignancies outside the central nervous system, compared with radiation therapy alone, as determined by objective response (brain and/or CAT scan) and/or increase in functional neurologic level and duration of response.

To determine the toxicity of multiple dose administration of metronidazole and radiation therapy.

Technical Approach:

The details are lengthy and specified in the original SWOG protocol. Duplicates are kept on file in the Clinical Investigation Department, WBAMC, and are available upon request.

Progress:

See Unit Summary.

Detail Summary Sheet

Date: 1 Oct 82 Prot No: 79/36 Status: Terminated  
Title:  
SWOG 7823/24/25/26: ROAP-ADOAP in Acute Leukemia, Phase III

Start Date: Est Comp Date:  
Principal Investigator: Facility:

LTC P.C. Farley, MC

Dept/Sec: Dept Medicine, Oncology Assoc Investigators  
Key Words:

Leukemia

Accumulative MEDCASE Est Periodic  
Cost OMA Cost: Review Results  
Study Objective:

To compare the efficacy of the 4-drug combination chemotherapy regimen, ROAP (Rubidazone, vincristine, arabinosyl cytosine, and prednisone) to ADOAP (the same combination using Adriamycin in place of Rubidazone) in adult acute leukemia, as determined by remission rate, remission duration and survival.

To determine the comparative toxicity of these regimens.

To determine whether late intensification therapy at 9 months after complete remission will improve long term, disease-free survival.

To determine whether immunotherapy using levamisole for 6 months after 12 months of complete remission on chemotherapy improves disease-free survival.

To determine reproducibility of the FAB/histologic classification and correlation to response to therapy in 200 consecutive cases of acute leukemia.

To study the effects of intensive supportive care in the management of acute leukemia.

Technical Approach:

The details are lengthy and specified in the original SWOG protocol. Duplicates are kept on file in the Clinical Investigation Department, WBAMC, and are available upon request.

Progress:

See Unit Summary.

# Detail Summary Sheet

Date: 1 Oct 82      Prot No: 80/8      Status: Completed

## Title:

Evaluation of Thyroid Hormones in Alcoholic Hepatitis

Start Date:

Est Comp Date:

Principal Investigator:

Facility:

MAJ M. Anees, MC

Dept/Sec: Dept of Medicine

Assoc Investigators

Key Words:

Thyroid hormones; alcoholism; hepatitis

Accumulative MEDCASE

Est

Periodic

Cost

OMA Cost:

Review Results

Study Objective:

The objective of this study is to delineate the physiology of thyroid hormone under the stress of alcoholic hepatitis. The intent is to determine if a defect in thyroid hormone metabolism exists and if so determine if the defect is a lack of deiodination of thyroxine (T4) or is a reversal of iodination.

## Technical Approach:

Twenty patients classified as acute alcoholic liver hepatitis will be entered into the study. Blood (10 ml) will be drawn on the day of admission for T4, T3, and rT3 studies. These studies will be repeated two more times at weekly intervals during the course of the hospital stay. Control studies will be performed on routine thyroid function study patients considered to be normal. Statistical comparison of normal versus test patient thyroid studies will be made and evaluated.

## Progress:

Thyroid functions: Serum T4, T3 RU, FTI, TBG and rT3 by RIA were obtained in 20 healthy volunteers (10 males and 10 females) and 22 patients hospitalized either for detoxification or complications of alcohol related liver disease, GI bleeding or ascites. Blood samples were drawn within 24 hours of admission. Six of 22 patients had moderately severe AH according to Adam and Foley's criteria.

Results showed normal T4, T3 RU, FTI and TBGs for all patients. T3 by RIA was not measured except in one patient; this was low at 44 pg/dl (Normal 59-201 pg/dl). The rT3 for the entire group was significantly higher than in the control group; however, the difference could be accounted for by the six patients with alcoholic hepatitis.



The high values of rT3 suggest that the body is trying to reduce  $O_2$  demanded by the liver by lowering T3 and shunting to rT3 to create a relatively hypometabolic state. Therapeutic induction of hypometabolism by propylthiouracil has been advocated by some workers. Our study seems to support the rationale of these researchers in the treatment of alcoholic hepatitis.

# Detail Summary Sheet

Date: 1 Oct 82 Prot No: 80/10 Status: Terminated

## Title:

The Hematologic & Metabolic Status of Sickie Cell Trait Individuals Following Vigorous Exercise

Start Date:

Est Comp Date:

Principal Investigator:

Facility:

LTC P.C. Farley, MC

Dept/Sec: Dept Medicine, Oncology

Assoc Investigators

Key Words:

Sickle Cell Trait

Accumulative MEDCASE

Est

Periodic

Cost

OMA Cost:

Review Results

Study Objective:

The degree of sickling, hemolysis, pH change, myolysis, and hematuria will be assessed in sickle cell trait individuals as compared to normal controls while undergoing vigorous exercise.

Technical Approach:

Approximately 50-70 heterozygous sickle hemoglobin patients and a like number of controls will be observed. The appropriate blood and urine studies will be performed on these individuals at their place of training while engaged in the physical activity. Individuals may be asked to participate more than once in the study if they demonstrate any departures from normal. The phases of investigation will be (a) screen incoming black recruit population for sickle cell trait and other heterozygous sickle cell states. (b) On volunteer controls and subject individuals obtain baseline CBC, serum chemistry, hemoglobin electrophoresis and urinalysis during in-processing. (c) Identify subgroups of study subjects according to the level of hemoglobin S and degree of hyposthenuria; load of physical conditioning and body habitus. (d) Contrast the subgroups of study participants with each other and with a control group while they undergo the PT test of their training program with the following parameters: Changes in CBC, electrolytes, muscle enzymes, serum free hemoglobin, and percent of sickling of red blood cells, urinary sediment content and assay of urine myoglobin and hemoglobin (e) Records to be kept - consent form of participants. Routine WBAMC data flow sheets will be used to record results. (f) During inprocessing of recruits we hope to ask their cooperation in joining the study and will present them with a consent form describing the

need to obtain blood and urine samples. Individuals who are asked to participate on more than one training occasion will be required to sign a consent for each occasion. (g) All of the above is to be coordinated with the training command.

**Progress:**

The principal investigator resigned. No patients were entered.

# Detail Summary Sheet

Date: 1 Oct 82 Prot No: 80/11 Status: Completed

Title:

Prospective Study of Mannitol in the Prevention of Radiographic Contrast Induced Acute Renal Failure

Start Date:

Est Comp Date:

Principal Investigator:

Facility:

MAJ M. Siedlecki, MC

Dept/Sec: Dept Medicine, Renal Clinic

Assoc Investigators

Key Words:

Mannitol; Radiographic contrast; Acute renal failure

Accumulative MEDCASE

Est

Periodic

Cost

OMA Cost:

Review Results

Study Objective:

The objective of this study is to perform a prospective, randomized and double-blind study of the possible protective effects of mannitol in preventing acute renal failure induced by radio contrast media.

## Technical Approach:

Approximately 20 subjects in each of two groups for each procedural category will be studied. The first procedure will be intravenous pyleography, but such procedures as coronary angiography abdominal and cranial angiography may also be studied. Patients will be ages 18 and above, active duty, dependents, and retired. The patients will be randomized blindly and either receive 500 cc of dextrose, 5 percent water or 500 cc of dextrose, five percent water plus five percent mannitol within one hour of the radiographic procedure. Additional volume supplementation will be at the discretion of the attending physician. The amount and type of contrast material used, and the type of procedure, as well as additional data, will be recorded.

## Progress:

The WBAMC Human Use Committee extended approval of this protocol to continue patient entry beyond the 20 originally proposed. Observations from this study have been published and presented (See FY80, FY81 and FY82 Table of Publications and Presentations).

Detail Summary Sheet

Date: 1 Oct 82 Prot No: 80/16 Status: Completed

Title:

An Investigation into the Effects of Cromolyn Sodium on Nonspecific Bronchial Hyperactivity

Start Date:

Est Comp Date: Mar 1982

Principal Investigator:

Facility:

LTC L.E. Mansfield, MC

Dept/Set: Dept Medicine, Allergy Clinic

Assoc Investigators

Key Words:

Cromolyn; Bronchial hyperactivity

Accumulative MEDCASE  
Cost

Est  
OMA Cost:

Periodic  
Review Results

Study Objective:

To evaluate whether cromolyn sodium administration will cause a decrease in non-specific airway hyper-reactivity. To determine if this diminution will be associated with a favorable clinical response.

Technical Approach:

Asthmatic patients will use cromolyn by inhalation in a double-blind cross-over trial. Bronchial hyper-reactivity will be monitored by monthly histamine challenges. Twenty nonpregnant adult asthmatic patients not requiring corticosteroid therapy will be selected. They will be advised of the purpose of the study and how it will be carried out. Any subject with a history suggesting a risk of renal or hepatic dysfunction will be excluded. This study will begin in October and end in March, at which time the code will be broken. If the results suggest significant benefit for cromolyn patients, the active therapy will be offered to all patients and the study continued for six more months.

Progress:

Thirty-six patients eventually completed this protocol. There were no significant adverse reactions. Pulmonary functions improved in the treated group as compared to the placebo group. Histamine sensitivity (nonspecific hyperreactivity) while showing a favorable direction for the treated group, did not demonstrate statistical difference. It is concluded that a longer time period may be required for the development of improved histamine tolerance. An abstract for presentation and a manuscript from this study are in preparation. A second longer term multicenter study has been initiated.

# Detail Summary Sheet

Date: 1 Oct 82 Prot No: 80/18 Status: Terminated

Title:

Clinical Evaluation of Renal Cortical Imaging Utilizing  $^{99m}\text{Tc}$ -Kidney Scintigraph

Start Date:

Est Comp Date:

Principal Investigator:

Facility:

LTC T.J. Brown, MC

Dept/Sec: Dept Medicine, Nuclear Med Svc Assoc Investigators

Key Words:

Renal Scanning

Accumulative MEDCASE

Est

Periodic

Cost

OMA Cost:

Review Results

Study Objective:

To determine the usefulness of  $^{99m}\text{Tc}$ -Kidney Scintigraph in studying renal blood flow and renal anatomy. Intended for use in high resolution and/or tomographic imaging for evaluation of anatomic detail. Especially important for space occupying lesions and renal trauma.

## Technical Approach:

A series of adult patients who require renal radionuclide studies for diagnostic purposes will be studied in detail and compared with our standard renal agents. The imaging protocol is as follows:

1. Rapid images of the kidneys will be obtained with an Anger Scintillation Camera during the first 30 seconds following injection of  $^{99m}\text{Tc}$ -DMSA. These views will be used to evaluate the agent as a vascular flow agent.

2. Initially static images will then be obtained over the kidneys for the next 15 to 30 minutes to qualitatively evaluate early renal uptake of radionuclide and to determine its usefulness as a fast renal imaging agent.

3. Initially sequential static images will also be obtained at varying time intervals to evaluate the optimal imaging time for this agent.

4. After the results of the above steps are evaluated in the first 20 patients, a modified imaging protocol will be developed for the remainder of the study based upon the usefulness of the early static images and optimal imaging time.

5. For individual patients, the standard posterior views will be supplemented by oblique, lateral, anterior and pinhole views as required.

The patients to be studied under this protocol will meet the following criteria: (1) Nonpregnant and over the age of 18, unless special indications for study exist. (2) All will have either known or suspected alteration of renal function or anatomic morphology, i.e., no subject without manifest or suspected disease will be studied

**Progress:**

Annual review of this protocol was conducted September 1982. The Human Use Committee was informed that DMSA was approved by the FDA on 18 Jun 82. No patients were entered on this protocol at WBAMC during FY82.

Detail Summary Sheet

Date: 1 Oct 82      Prot No: 80/19      Status: Terminated

Title:

WRAMC 7915 Prevention of Gonadal Damage in Women Treated with  
Combination Chemotherapy or Radiotherapy Below the Diaphragm for  
Hodgkins or nonHodgkins Lymphoma

Start Date:

Est Comp Date:

Principal Investigator:

Facility:

LTC P.C. Farley, MC

Dept/Sec: Dept Medicine, Oncology

Assoc Investigators

Key Words:

Lymphoma; Ova; Gonad

Accumulative MEDCASE

Est

Periodic

Cost

OMA Cost: \$152(152)

Review Results

Study Objective:

To protect the ova and follicular cells from ionizing radiation or  
chemotherapeutic damage and death by putting these cells at rest  
during active therapy.

Technical Approach:

The details are lengthy and specified in the original WRAMC  
protocol. Duplicates are kept on file in the Clinical Investigation  
Department, WBAMC, and are available upon request.

Progress:

None.



Detail Summary Sheet

Date: 1 Oct 82 Prot No: 80/20 Status: Terminated  
Title:  
SWOG 7827: Combined Modality Therapy for Breast Carcinoma, Phase III

Start Date: Est Comp Date:  
Principal Investigator: Facility:

LTC P.C. Farley, MC

Dept/Sec: Dept Medicine, Oncology Assoc Investigators  
Key Words:

Carcinoma, breast

Accumulative MEDCASE Cost	Est OMA Cost:	Periodic Review Results
Study Objective:		

1. To compare the disease-free interval and recurrence rates in estrogen receptor positive (ER+) premenopausal patients with Stage II disease, using combination chemotherapy alone versus combination chemotherapy and oophorectomy.
2. To compare the disease-free interval and recurrence rates in estrogen receptor positive postmenopausal patients with Stage II disease, using combination chemotherapy plus tamoxifen versus tamoxifen alone versus combination chemotherapy alone.
3. To compare the disease-free interval and recurrence rates in all estrogen receptor negative (ER-) patients with Stage II disease using one versus two years of combination chemotherapy.
4. To compare the effect of these various adjunctive therapy programs upon the survival patterns of such patients.
5. To correlate the ER status with disease-free interval and survival.

Technical Approach:

The details are lengthy and specified in the original SWOG protocol. Duplicates are kept on file in the Clinical Investigation Department, WBAMC, and are available upon request.

Progress:

See Unit Summary.

Detail Summary Sheet

Date: 1 Oct 82 Prot No: 80/21 Status: Terminated

Title:

SWOG 7927/28: Chemotherapy for Multiple Myeloma Phase III

Start Date:

Est Comp Date:

Principal Investigator:

Facility:

LTC P.C. Farley, MC

Dept/Sec: Dept Medicine, Oncology

Assoc Investigators

Key Words:

Multiple myeloma

Accumulative MEDCASE

Est

Periodic

Cost

OMA Cost:

Review Results

Study Objective:

1. To compare the effectiveness of four different drug combinations for remission induction in previously untreated patients with multiple myeloma. Results will also be compared with those from similar therapies in recently completed Southwest Oncology Group Studies.

2. For patients with a 75 percent tumor reduction; to evaluate the role of 12 months of chemotherapy maintenance with VCP or VCP plus levamisole, when compared with previous experiences.

Technical Approach:

The details are lengthy and specified in the original SWOG protocol. Duplicates are kept on file in the Clinical Investigation Department, WBAMC, and are available upon request.

Progress:

See Unit Summary.

# Detail Summary Sheet

Date: 1 Oct 82 Prot No: 80/22 Status: Terminated

## Title:

SWOG 7924: Multimodal Therapy for Limited Small Cell Carcinomas of the Lung

Start Date:

Est Comp Date:

Principal Investigator:

Facility:

LTC P.C. Farley, MC

Dept/Sec: Dept Medicine, Oncology

Assoc Investigators

Key Words:

Carcinoma, lung

Accumulative MEDCASE  
Cost

Est  
OMA Cost:

Periodic  
Review Results

Study Objective:

1. To determine the efficacy of sequentially alternating, mutually noncross-resistant, multidrug regimens in remission induction and intensification therapy in patients with limited small cell lung carcinoma.
2. To determine the value of chest-radiotherapy added to intensive systemic chemotherapy in reducing chest recurrences, and in improvement of survival.
3. To determine the relative efficacy and toxicity of low-dose, extensive chest radiation when used in close chronologic sequence with systemic multiagent chemotherapeutic regimens.
4. To determine whether radiotherapy ports should be set according to tumor size prior to or after induction chemotherapy.
5. To determine the value of combined systemic chemotherapy and radiotherapy in the control of bulky chest disease.

Technical Approach:

The details are lengthy and specified in the original SWOG protocol. Duplicates are kept on file in the Clinical Investigation Department, WBAMC and are available upon request.

Progress:

See Unit Summary

Detail Summary Sheet

Date: 1 Oct 82      Prot No: 80/23      Status: Terminated

Title:

An Evaluation of Three Rapid Nonradioisotopic Methods for the Immune Complexes in Human Disease

Start Date:

Est Comp Date:

Principal Investigator:

Facility:

LTC L.E. Mansfield, MC

Dept/Sec: Dept Medicine, Allergy Clinic      Assoc Investigators

Key Words:

Enzyme linked immunoassay; Nephelometry; Latex agglutination inhibition; Radioimmunoassay

Accumulative MEDCASE

Est

Periodic

Cost

OMA Cost:\$352(666)

Review Results

Study Objective:

To evaluate three different methods to detect immune complexes in human disease. It is hoped to find the one or two most useful methods through clinical research and in patient surveillance.

Technical Approach:

Three methods will be used to measure immune complexes: laser nephelometer, an enzyme linked assay, and latex agglutination inhibition. These will be compared to C<sub>1</sub>Q radioimmunoassay in their ability to detect preformed human immune complexes.

Progress:

Progress was made in the refinement of the enzyme linked assay. These techniques are being applied to other protocols and will be carried forward under those protocols.

# Detail Summary Sheet

Date: 1 Oct 82 Prot No: 80/24 Status: Completed

## Title:

The Development of an Enzyme Linked Assay to Measure Human Allergen Specific Antibodies of the Immunoglobulins G and M Class

Start Date:

Est Comp Date:

Principal Investigator:

Facility:

LTC L.E. Mansfield, MC

Dept/Sec: Allergy Clinic

Assoc Investigators

Key Words:

Immunoglobulins; Enzyme linked immunoassay

Accumulative MEDCASE

Est

Periodic

Cost \$4,600

OMA Cost: \$1325(\$5847)

Review Results

Study Objective:

To modify the enzyme linked immunoassay developed to measure allergen specific IgE antibodies to the measurement of allergen specific IgG and IgE antibodies.

## Technical Approach:

Allergen will be chemically bound to polyethylene tubes or plastic microtiter plates. Highly specific rabbit antisera to IgG and IgM will have either alkaline phosphatase or galactosidase enzyme attached to it. The plates or tubes will be layered over with human allergic sera obtained at various times during allergen immunotherapy.

They will be washed and then relayered with "labeled" anti IgG or IgM. After incubation the plates or tubes will be washed. A solution containing the proper substrates for the enzyme will be added to the plates. The enzyme driven reaction will cause a colorimetric change in the solution. The results will be read visually and in a spectrophotometer. The results will be compared to the radioimmunoprecipitation method which will be performed in the usual fashion. The human sera used has been previously obtained and evaluated by the radioimmunoprecipitation at Fitzsimons Army Medical Center.

## Progress:

The techniques for this study have been developed and are being utilized in a variety of protocols detailed elsewhere in this report.

# Detail Summary Sheet

Date: 1 Oct 82 Prot No: 80/26 Status: Completed

## Title:

Assessment of Hematologic and Neurologic Abnormalities in the Young Alcoholic Patient

Start Date:

Est Comp Date:

Principal Investigator:

Facility:

LTC P.C. Farley, MC

Dept/Sec: Dept Medicine, Oncology

Assoc Investigators

Key Words:

Alcoholism

Accumulative MEDCASE

Est

Periodic

Cost

OMA Cost: \$788(788)

Review Results

Study Objective:

To determine if hematologic abnormalities exist in the young alcoholic population in the absence of liver disease or severe nutritional deficiency. To determine the degree of intellectual impairment and presence of peripheral neuropathies especially in the young alcoholic patient.

## Technical Approach:

All patients admitted for alcohol detoxification or alcoholic liver disease will be considered study subjects. No invasive procedures as bone marrow biopsy or liver biopsy will be proposed as part of this study. However, if the patient's physician obtains such a biopsy, we will use the data. CBC, SMA 12, serum folate and blood smear will be obtained routinely. Patients who are anemic will have a red cell folate and serum Fe and IBC also collected, and other studies as indicated to evaluate the anemia. In addition to the above routine evaluation, the patients will be asked to consent to the following: (1) Liver sonogram study, (2) Clinical examination by neurologist, (3) Cranial C.T. Scan (when machine is available at WBAMC), (4) WAIS Test (Weckler Adult Intelligence Scale). Most patients consent to enter the Day Care Treatment Center for two weeks after admission for detoxification. Ideally this will be the period of time when studies are obtained.

## Progress:

The Drug and Alcohol Treatment Center of Fort Bliss, TX referred 160 consecutive active duty subjects for our study after voluntary consent was obtained. A history of general health was obtained, and alcohol and smoking history were specifically elicited. Patients with a history of drug abuse only were excluded. A physical examination to detect signs of hepatomegaly or skin changes such as seen in liver disease, and signs of peripheral neuropathy were specifically sought. Laboratory evaluation included complete blood count (CBC) and SMA-12 in all subjects. The first 30 subjects also submitted a sample for red cell folate, serum folate, serum B-12, and serum iron and iron binding capacity. After excluding patients with thalassemia minor or other anemia and patients with incomplete laboratory data, 142 subjects remained for analysis.

A control group of 100 active duty personnel presenting as donors to the William Beaumont Army Medical Center Blood Bank were elicited as volunteers. Personal interviews were not conducted on the controls. A questionnaire was used to elicit age and drinking and smoking history to include amount, type and frequency of alcohol consumption and tobacco use. Name or other identifying data were excluded from the questionnaire to maximize confidentiality and encourage frankness. A CBC was obtained to match each questionnaire. Subjects with thalassemia minor were excluded and none were anemic. The drinking habit in both referral cohort and controls were grouped as follows: Group I - non-drinker or light social drinker. Group II - an intake of six 12 ounce cans of beer or one quart of wine or six ounces of liquor on two days per week or a couple of drinks or beers on an almost daily basis. Persons who had less than the minimum defined in Group II or who engaged in heavy drinking of any amount less often than one day a week were included in Group I.

The tobacco use habit was grouped as follows: Group I - nonsmokers, exsmokers greater than six months duration, cigar and pipe smokers who never smoked cigarettes. Cigarette smokers using less than one-half package of cigarettes daily were included in Group I. Group II - All cigarette smokers using greater than one-half package daily, and former cigarette smokers who now use a pipe or cigars regularly.

A distinct difference in the history obtained from younger and older subjects of the referral group arbitrarily defined as under 30 and over 30 years of age respectively was noted. Younger subjects generally were self-referred; some were referred by a supervisor. They exhibited no paranoia about divulging the alcohol history, and consequently claimed to drink more than the over 30 group as a whole. The older group were most coerced into entering the alcohol

treatment program by supervisors or associates and tended to minimize their alcohol habit during the interview. Nearly all the heavier drinkers smoked cigarettes daily and chronic bronchitis was a frequently associated complaint when inquired about. A history of liver disease, alcoholic seizures or alcohol withdrawal symptoms requiring treatment was very rare.

No overt signs of alcoholic liver disease as manifested by skin findings, clear hepatomegaly, or characteristic body habitus were found in any patient under 40 years old. A few older patients having such findings were hospitalized for further evaluation and excluded from analysis if found to be anemic. No findings of peripheral neuropathy were found in anyone under 40 years of age.

The mean corpuscular volume (MCV) of the red blood cell was strongly correlated with age and with drinking and smoking history. The entire group of 242 subjects had a mean MCV of  $84.35 + 0.255x$  the age in years by linear regression of the MCV on age.

Smoking history was analyzed separately in the control group using the standard F test for comparison of two regression lines. Nearly parallel slopes exist for light smokers and heavy smokers, and heavy smokers with the Y intercept at MCV 86.67 and MCV 88.02 respectively. This demonstrates that whereas the MCV is shifted upward on the Y axis for heavy smokers compared to light smokers, the normal rate of rise with age is maintained in smokers.

Drinking history must be analyzed coexistent with smoking as nearly all drinkers were smokers. When contrasting the Groups I and II by drinking history, nonparallel lines emerge ( $p=0.03$ ). The Group I has Y intercept of 86.48 and slope of 0.144, whereas the Group II has a Y intercept of 90.9 and slope of 0.06. We can conclude that heavy alcohol use raises the MCV to a nearly maximal amount at an early age, and the slope of increase is slight with advancing age when heavy drinking and smoking are covariants.

The serum and red cell folate levels and serum B12 levels were normal in the first 30 patients, so these assays were not obtained in the following patients. A clear trend toward higher values for AST and GGT existed in drinkers as opposed to nondrinkers, but the range in findings was highly variable. These two enzymes do not appear to be useful parameters of the alcohol habit in this group of young adults.



Detail Summary Sheet

Date: 1 Oct 82      Prot No: 80/28      Status: Terminated

Title:

The Use of a New Multitest Applicator in the Evaluation of the Clinical Efficacy of Allergen Immunotherapy

Start Date:

Est Comp Date:

Principal Investigator:

Facility:

LTC L.E. Mansfield, MC

Dept/Sec: Dept Medicine, Allergy Clinic      Assoc Investigators

Key Words:

Immunotherapy

Accumulative MEDCASE

Est

Periodic

Cost

OMA Cost:

Review Results

Study Objective:

To assess the value of using a new device called the multitest in the use of serial skin tests to monitor the efficacy of allergen immunotherapy.

Technical Approach:

Thirty adult patients who are to begin immunotherapy will be entered into the study. The nature and the purpose of the study will be explained to them.

Each patient will have an immunotherapy set prepared for them. This will be that which is clinically indicated for them. On the day when they begin their immunotherapy program, they will have a specimen of blood drawn. They will be tested by the prick-puncture and by the multitest device to the following: 10 serial dilutions 1:200 to 1:200,000 for their treatment mixture; dilutions of 1:100 to 1:100,000 of either ragweed or Russian thistle allergen (depending upon the patient's sensitivity). The multitest device will be placed so that the top part of the device touches an imaginary line drawn through the points of the scapula. A template will be used to assure a constant location for the titrated puncture test. For uniformity prick-puncture test will be done on the right side of the back two inches from the spine. The serum obtained prior to immunotherapy and at maintenance will be evaluated for the presence of IgE, IgG, and IgM specific antibody to ragweed and/or Russian thistle allergen.

Progress: None.

# Detail Summary Sheet

Date: 1 Oct 82 Prot No: 80/31 Status: Completed

## Title:

Direct and Indirect Radionuclide Cystography in the Detection of Vesicoureteral Reflux

## Start Date:

Est Comp Date:

Principal Investigator:

Facility:

LTC T.J. Brown, MC

Dept/Sec: Dept Medicine, Nuclear Med Svc Assoc Investigators

## Key Words:

Cystography; Vesicoureteral reflux

Accumulative MEDCASE

Est

Periodic

Cost

OMA Cost:

Review Results

## Study Objective:

1. To detect and quantify vesicoureteral reflux.
2. To provide early detection of any deterioration in renal function.

## Technical Approach:

Patients with known vesicoureteral reflux will be studied by computerized radionuclide renal imaging and direct radionuclide cystography. The radioactive pharmaceutical used will be <sup>99m</sup>Tc-DTPA. These studies will be performed on the child's regularly scheduled followup visit to the Urology Clinic, in lieu of further radiographic examinations. A flow sheet will be completed on each child that is studied and copies retained by the Nuclear Medicine and Urology Service.

## Progress:

The data indicated satisfactory diagnostic capabilities of the radionuclide to detect vesicoureteral reflux. The study is now offered as a routine procedure by the Nuclear Medicine Service.

Detail Summary Sheet

Date: 1 Oct 82 Prot No: 80/32 Status: Completed

Title:

A Randomized Trial of Chemotherapy and Radiation Versus Radiation Alone in the Treatment of Advanced Non-small Cell Lung Cancer

Start Date:

Est Comp Date:

Principal Investigator:

Facility:

LTC P.C. Farley, MC

Dept/Sec: Dept Medicine, Oncology Cl

Assoc Investigators

Key Words:

Carcinoma, lung

Accumulative MEDCASE  
Cost

Est  
OMA Cost:

Periodic  
Review Results

Study Objective:

To determine the efficacy of combination chemotherapy with 5Fu, Vincristine and Mitomycin as measured by response rate and survival benefit in patients with advanced non-small cell lung cancer.

Technical Approach:

The details are lengthy and specified in the original protocol. Duplicates are kept on file in the Clinical Investigation Department, WBAMC, and are available upon request.

Progress:

Thirteen patients were entered into this study. There was a 10.4 month average survival time utilizing this regimen. Conclusions are being prepared for publication.

# Detail Summary Sheet

Date: 1 Oct 82 Prot No: 80/33 Status: Complete  
 Title:  
 The Effect of Beta 2-Adrenergic Agents on Immunoglobulins

Start Date: Est Comp Date:  
 Principal Investigator: Facility:

LTC L.E. Mansfield, MC

Dept/Sec: Dept Medicine, Allergy Clinic Assoc Investigators  
 Key Words:

Beta II agonists; Immunoglobulins

Accumulative MEDCASE	Est	Periodic
Cost	OMA Cost:\$1687(4534)	Review Results
Study Objective:		

To establish in an animal model if the effects of beta-2-adrenergic agents on immunoglobulin levels are due to defects of synthesis or increased catabolism.

## Technical Approach:

Laboratory white rats will be used for this experiment. They will be grouped in units of ten animals according to the following plan.

- Control groups, no medication
- Terbutaline 125 mcg/kg twice daily for 4 weeks
- Terbutaline 200 mcg/kg twice daily for 4 weeks
- Terbutaline 500 mcg/kg twice daily for 4 weeks
- Isoproterenol 375 mcg/kg twice daily for 4 weeks

One week prior to beginning medications all animals will be immunized with human gamma globulin (HGG). Just prior to beginning the medication blood will be drawn and IgG, IgM, and IgA levels will be measured. Antibody titer to HGG will be determined. On the seventh day of the medication regimen the rats will be given a booster of HGG along with a primary immunization of KLH. After the fourth week of therapy the rats will have blood taken for the determination of immunoglobulin, secondary response to HGG and primary response to KLH. Immunoglobulins will be measured by passive hemagglutination and radial immunodiffusion. Antibodies will be determined by passive hemagglutination.

Progress: This study was extended because of some questions regarding early methodology of measuring antibody response. During the second phase of the experiment, the preliminary findings of the first phase were confirmed. Terbutaline use on a daily basis of 10-25 micrograms per kg per rat was associated with inhibition of both the primary and secondary antibody response. Higher doses of terbutaline did not demonstrate this effect. This material is being submitted for presentation and a manuscript is in preparation. Furthermore, several successful protocols involving cell mediated immunity in animals and humans, and the effects of terbutaline were a natural outgrowth of this study.

Detail Summary Sheet

Date: 1 Oct 82 Prot No: 80/35 Status: Terminated

Title:

SWOG 7965: Treatment of Early Squamous Cell Ca of the Head and Neck with Initial Surgery and/or Radiotherapy Followed by Chemotherapy vs No Further Treatment Phase III

Start Date:

Est Comp Date:

Principal Investigator:

Facility:

LTC P.C. Farley, MC

Dept/Sec: Dept Medicine, Allergy Clinic Assoc Investigators

Key Words:

Carcinoma, head and neck

Accumulative MEDCASE

Est

Periodic

Cost

OMA Cost:

Review Results

Study Objective:

To determine if the disease-free interval and survival of patients in high risk categories of squamous head and neck cancer can be improved by adjuvant methotrexate after initial surgery, radiotherapy or both have resulted in no clinically evident disease (N.E.D)

Technical Approach:

The details are lengthy and specified in the original SWOG protocol. Duplicates are kept on file in the Clinical Investigation Department, WBAMC, and are available upon request.

Progress:

See Unit Summary.

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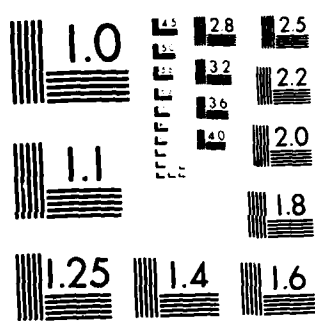
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F/G 6/5

NL

A 10x10 grid of squares. The top-left corner is missing a 2x2 block of squares, resulting in a total of 98 squares. The grid is composed of 10 rows and 10 columns. The first two rows have 9 squares each, and the remaining eight rows have 10 squares each.



MICROCOPY RESOLUTION TEST CHART  
NATIONAL BUREAU OF STANDARDS-1963-A



# Detail Summary Sheet

Date: 1 Oct 82      Prot No: 80/36      Status:      erminated

## Title:

SWOG 7902: Combined Modality Therapy with Chemotherapy Radiotherapy and Surgery in Advanced Previously Untreated (Unresectable) Stage III and IV Epidermoid Cancer of the Head and Neck, Phase III

Start Date:

Est Comp Date:

Principal Investigator:

Facility:

LTC P.C. Farley, MC

Dept/Sec: Oncology

Assoc Investigators

Key Words:

Carcinoma, head and neck

Accumulative MEDCASE

Est

Periodic

Cost

OMA Cost:

Review Results

Study Objective:

To compare the survival of Stage III and IV squamous cell carcinoma of the tongue, oral cavity, tonsil, oropharynx, hypopharynx and larynx subjected to radiation therapy followed by surgical excision if possible, versus survival of patients subjected to chemotherapy with Cis-Platinum Oncovin, and Bleomycin (COB), followed by radiation therapy and surgical versus radiotherapy and head and neck surgery.

Technical Approach:

The details are lengthy and specified in the original SWOG protocol. Duplicates are kept on file in the Dept Clinical Investigation, WBAMC, and are available upon request.

Progress:

See Unit Summary.

Detail Summary Sheet

Date: 1 Oct 82	Prot No: 80/37	Status: Terminated
Title:		

SWOG 7808: Combination Modality Treatment for Stage III and IV Hodgkins Disease MOPP 6, Phase III

Start Date:	Est Comp Date:
Principal Investigator:	Facility:

LTC P.C. Farley, MC

Dept/Sec: Oncology	Assoc Investigators
Key Words:	

Lymphoma; Spermatozoa; Gonad

Accumulative MEDCASE Cost	Est OMA Cost:	Periodic Review Results
Study Objective:		

1. To attempt to increase the complete remission rate induced with MOP-BAP alone utilizing involved field radiotherapy in patients with Stage III and IV Hodgkin's disease achieving a PR at the end of six cycles of MOP-BAP.

2. To determine if immunotherapy maintenance with levamisole or consolidation with low dose involved field radiotherapy will produce significantly longer remission duration over a no further treatment group when CR has been induced with six cycles of MOP-BAP in Stages III and IV Hodgkin's disease.

Technical Approach:

The details are lengthy and specified in the original SWOG protocol. Duplicates are kept on file in the Dept Clinical Investigation, WBAMC, and are available upon request.

Progress:

See Unit Summary.

Detail Summary Sheet

Date: 1 Oct 82      Prot No: 80/38      Status: Terminated

Title:

SWOG 7983: Radiation Therapy in Combination w/CCNU in Patients with Incompletely Resected Gliomas of the Brain Grade I and II, Phase III

Start Date:

Est Comp Date:

Principal Investigator:

Facility:

LTC P.C. Farley, MC

Dept/Sec: Oncology

Assoc Investigators

Key Words:

Glioma

Accumulative MEDCASE  
Cost

Est  
OMA Cost:

Periodic  
Review Results

Study Objective:

1. The major objective of this study is to compare the survival of patients with incompletely resected Grade I and II gliomas treated with radiation alone versus radiation and CCNU.

2. To compare the effectiveness of radiation therapy versus radiation therapy plus CCNU for remission induction and duration of remission. Because many of these patients will have poorly or non-measurable disease, this will only be a secondary objective.

Technical Approach:

The details are lengthy and specified in the original SWOG protocol. Duplicates are kept on file in the Dept Clinical Investigation, WBAMC, and are available upon request.

Progress:

None.

Detail Summary Sheet

Date: 1 Oct 82      Prot No: 80/39      Status: Terminated  
Title:

SWOG 7985: Combined Modality Treatment for ER-Breast Cancer,  
Phase III

Start Date:      Est Comp Date:  
Principal Investigator:      Facility:

LTC P.C. Farley, MC

Dept/Sec: Oncology      Assoc Investigators  
Key Words:

Carcinoma, Breast

Accumulative MEDCASE      Est      Periodic  
Cost      OMA Cost:      Review Results

Study Objective:

To compare disease-free interval and survival among control group Stage I (and Stage II node negative) breast cancer patients whose tumors are determined to be ER- at the time of mastectomy, versus Stage I (and Stage II node negative) ER- patients treated with adjuvant CMFV for six months.

To document recurrence patterns among untreated patients with Stage I breast cancer whose tumors are determined to be ER- at the time of mastectomy.

Technical Approach:

The details are lengthy and specified in the original SWOG protocol. Duplicates are kept on file in the Dept Clinical Investigation, WBAMC, and are available upon request.

Progress:

None.

# Detail Summary Sheet

Date: 1 Oct 82 Prot No: 80/40 Status: Completed  
Title:

Exercise Induced Asthma in Basic Trainees

Start Date: Est Comp Date:  
Principal Investigator: Facility:

LTC S.R. Smith, MC

Dept/Sec: Dept Medicine Assoc Investigators  
Key Words:

Asthma

Accumulative MEDCASE Est Periodic  
Cost \$18,050 OMA Cost: Review Results

Study Objective:

This study is undertaken to determine the incidence of exercise induced asthma in basic trainees. The study will attempt to identify these individuals by pulmonary function testing and the American Thoracic Society questionnaire.

Technical Approach:

Each BCT recruit will fill out an ATS-DLD 78 questionnaire regarding his family, personal and medical history. Standardization of this questionnaire has previously been accomplished. While being held in the reception station, Fort Bliss, each recruit will undergo pulmonary function testing. Those individuals with subtle spirometric abnormalities (i.e. reduced mid and terminal flows) or with a mild obstructive ventilatory defect will undergo exercise testing. For the purpose of this study the grading system devised by the Committee on Pulmonary Physiology, American College of Chest Physicians will be followed. Although extensively used as clinical recommendations, the sensitivity and specificity of the questionnaires and pulmonary function tests are conjectural. Statistical analyses will follow available guidelines. Exercise testing will be carried out on a bicycle ergometer. Exercise workloads will be increased 25 watt seconds each minute. During the last 15 seconds of each minute period, the heart rate, minute ventilation test will be continued until a heart rate of eighty percent of the age adjusted maximum heart rate is attained or until the patient fatigues. During exercise, oxygen saturation will be monitored with an ear oximeter. If oxygen saturation drops below 75 percent, the study will be stopped. Spirographic tracings will be

done at 5, 15 and 25 minutes after cessation of exercise as well as at 10 minutes after inhaled bronchodilators. After basic training all individuals will again complete the ATS-DLD questionnaire. Any individuals with new symptoms will be re-evaluated. Retrospective analysis of preinduction pulmonary functions and questionnaires will be carried out to determine if any single factor predicts exercise induced asthma during basic training. Pulmonary function tests will be compared with the normals established by the VA-Army study.

Progress:

Over 400 recruits were studied. No "occult" asthmatics were discovered. During the duration of the study no request for medical boards with the diagnosis of asthma were submitted. Following the study, the requests returned to the usual rate. An abstract is in preparation.

Detail Summary Sheet

Date: 1 Oct 82      Prot No: 80/41      Status: Terminated  
Title:

WRAMC 7810: Prevention of Gonadal Damage in Men Treated with  
Combination Chemotherapy/Radiotherapy for Hodgkins Disease and  
non-Hodgkins Lymphomas

Start Date:      Est Comp Date:  
Principal Investigator:      Facility:

LTC P.C. Farley, MC

Dept/Sec: Oncology Svc      Assoc Investigators  
Key Words:

Lymphoma; Spermatozoa, gonad

Accumulative MEDCASE      Est      Periodic  
Cost      OMA Cost:      Review Results  
Study Objective:

To prevent permanent infertility and alterations in normal sexual  
function caused by combination chemotherapy in the treatment of  
Hodgkin's disease or non-Hodgkin's lymphoma.  
Technical Approach:

The details are lengthy and specified in the original WRAMC  
protocol. Duplicates are kept on file in the Dept Clinical  
Investigation, WBAMC, and are available upon request.

Progress:

None.

### Detail Summary Sheet

Date: 1 Oct 82      Prot No: 81/04      Status: Completed  
Title:

Can Nuclear Scanning Predict Resolution of Osteomyelitis

Start Date:      Est Comp Date:  
Principal Investigator:      Facility:

CPT G. Graham, MC

Dept/Sec:      Nuclear Medicine      Assoc Investigators  
Key Words:

Bone scanning; Osteomyelitis

Accumulative MEDCASE      Est      Periodic  
Cost      OMA Cost: \$680(1079)      Review Results  
Study Objective:

To determine the sensitivity of Tc-PyP bone scan to follow the resolution of osteomyelitis under treatment.

#### Technical Approach:

After anesthetizing rabbits with IV ketamine, right and left rear legs will be surgically prepared. Right and left legs will be randomized, treated and untreated. Control animals will not be the same rabbit as treated rabbit.

The right rear leg will be injected percutaneously through the lateral aspect of the metaphysis of the tibia into the medullary cavity with 0.01 cc of a sclerosing agent (Five percent sodium morrhuate) and a 0.01cc of a suspension of Staphylococcus aureus.

The left rear leg will be injected percutaneously as above and 0.01cc of the sclerosing agent and 0.01cc of normal saline will be instilled.

A technetium scan will be done on both legs at two and four weeks. Concerning the right rear leg, blind readings will be made. The physician reading the scan will not know which leg was used nor whether the animal is treated or untreated.

(1) If the scan remains negative at four weeks, the animal will be sacrificed and the right tibia cultured.

(2) If the scan becomes positive the animal will be treated and scans will be repeated at two week intervals. If the scan becomes



negative the animal will be sacrificed and the tibia cultured. If the scan remains positive beyond eight weeks the animal will be sacrificed and the marrow will be cultured.

Concerning the left rear leg: If the scan remains negative at four weeks, further study will be done of the area. If the scan becomes positive the animal will be sacrificed irregardless of the right leg study, and the left tibia cultured to determine the etiology of the positive scan.

#### Progress:

Sixty-six rabbits were injected with a suspension of Staphylococcus aureus and sodium morrhuate in the right tibia. After four weeks 49 rabbits developed osteomyelitis and were treated with antibiotics. A gallium-67 scintigram was obtained every two weeks for up to ten weeks during treatment. During these ten weeks of treatment 51% (25/49) developed negative gallium-67 scintigrams and were sacrificed. All 25 with negative gallium-67 scintigrams had negative bacteriologic cultures of the right tibia. At the end of ten weeks after the initiation of antibiotics, the 18 rabbits with persistently positive scintigrams were sacrificed. Eleven of these had positive bacteriologic cultures of the tibia while seven were negative. This data suggests that sequential gallium-67 scintigrams may be useful in predicting the cure of osteomyelitis during treatment.

# Detail Summary Sheet

Date: 1 Oct 82      Prot No: 81/05      Status: Ongoing  
Title:

The Role of Food Allergy in the Pathogenesis of Migraine Headache

Start Date:      Est Comp Date:  
Principal Investigator:      Facility:

LTC L.E. Mansfield, MC

Dept/Sec: Allergy Clinic      Assoc Investigators  
Key Words:

Food allergy; Migraine headache

Accumulative MEDCASE      Est      Periodic  
Cost      OMA Cost:      Review Results

Study Objective:

Assess whether skin testing to a battery of food allergens is of value in defining a diet which will cause a decreased frequency of migraine headaches in affected patients.

Technical Approach:

Subjects will be 18 years or older. They will be selected from the population of the Neurology Clinic, WBAMC. They will be judged by one of the investigators to have migraine syndrome. The nature, the purpose, and proposed benefits of the study will be explained to them. If they are agreeable, the following will be done: (1) Any medications being used for chronic migraine prophylaxis will be discontinued. (2) They will be given a supply of medication for acute migraine attacks. (3) They will report to the Allergy Clinic where the following will be performed:

- a. A history regarding possible food provoked migraine.
- b. Prick puncture testing on the back to 75 common foods.
- c. A diet will be prescribed avoiding those foods which are positive on skin testing (2 mm wheal greater than control).
- d. A small blood serum specimen (5 ml) will be collected and frozen for later use if required.

If there are no positive skin tests, the patient will be placed on a corn, egg, milk, wheat free diet. The duration of the diet will be eight weeks. The patients will record symptoms and medications on the diary sheets. Each four weeks the patients will meet with one of the investigators. At the end of eight weeks those who appeared to have had a positive response, that is complete absence of attacks or a greater than 50 percent diminution, will remain on the diet.

Those patients will then undergo a double-blind challenge supervised by one of us. All of the materials for the challenges will be prepared by the other investigator and his staff. The challenge shall be performed in the following manner. Patients will be given a group of opaque capsules containing placebo or freeze-dried foods. The foods chosen will be according to what was eliminated. Interspaced with the foods will be capsules containing placebo (lactose). The maximum amount of challenge food given in one day will be 8 gms. They will take these capsules on a daily basis. This diet challenge period will be individualized for each patient, and may vary in duration. Patients will continue to complete the diary sheets and be seen every four weeks.

Criteria for evaluation of the results will be:

- a. Definitely positive: Significant relief of migraine attacks and positive challenges.
- b. Possible positive response: One of the challenges positive, one negative, diet trial yields relief.
- c. Equivocal placebo effect: Diet trial yields good response in relief of headaches; challenges are negative.
- d. Negative: No relief with the diet trial.

**Progress:**

Fifty-five patients have been entered and are currently being followed. Five patients have demonstrated unequivocal migraine response to double blind food challenge. Additional patients are being entered.

# Detail Summary Sheet

Date: 1 Oct 82	Prot No: 81/08	Status: Terminated
Title:		

Accuracy of Equilibrium ECG Gated Blood Pool Study in Following Cardiac Improvement with Afterload Reduction in CHF

Start Date:	Est Comp Date:
Principal Investigator:	Facility:

CPT R.D. Latham, MC

Dept/Sec: Dept Medicine	Assoc Investigators
Key Words:	

Accumulative MEDCASE	Est	Periodic
Cost	OMA Cost:	Review Results

Study Objective:

To determine if noninvasive multiple gated acquisition studies (MUGA) are as accurate as Swan-Ganz catheterization to assess cardiac improvement in patients with CHF begun on afterload reduction.

Technical Approach:

Subjects will be patients admitted to Coronary Care Unit in CHF and in whom C, Cardiology agrees afterload reduction would be beneficial in the management of the patient. Patients will meet the following criteria for CHF (congestive heart failure);

(1) Cardiomegaly, a S<sub>3</sub> gallop and normal sinus rhythm by physical examination.

(2) Measured CI less than 3.0, PCWP more than 15

In addition, the primary physician must consider the patient a candidate for vasodilator therapy. Afterload reduction is therapy with standard drugs such as hydralazine which result in vasodilatation.

(b) Patients will receive standard coronary care unit care and monitoring.

(c) Swan-Ganz thermodilution catheters will be utilized and placed in routine fashion.

(d) Hemodynamic data from Swan-Ganz catheter will be obtained at least every twelve hours.

(e) The only alteration of a patient's routine care will be a portable equilibrium ECG gated blood pool study performed every morning when the Swan-Ganz parameters are obtained. More frequent scans b.i.d. are at the discretion of principal or associate investigator. No more than six scans will be performed on a single patient.

(f) The data obtained will be maintained on a daily flow sheet.

(g) The degree of correlation will be determined by standard biostatistical analysis regressing Swan-Ganz values against those obtained by MUGA scans.

PROGRESS: None

# Detail Summary Sheet

Date: 1 Oct 82 Prot No: 81/09 Status: Terminated  
Title:

The Usefulness of Modern Clinical Immunologic Testing in the Prediction of Disease, a Pilot Study

Start Date: Est Comp Date:  
Principal Investigator: Facility:

LTC L.E. Mansfield, MC

Dept/Sec: Allergy Clinic Assoc Investigators  
Key Words:

COL L.L. Penney, MC

Accumulative MEDCASE Est Periodic  
Cost OMA Cost: \$50 Review Results

Study Objective:

To determine if a one-time global immune evaluation can be used as a predictor of future disease.

Technical Approach:

Twenty active duty soldiers will be selected for this study. The basis of their selection will be a decision by the Physicians in the Troop Medical Clinic that the amount of illnesses of a nontraumatic nature, or nonpsychological nature, experienced by this service member is greater than expected by his peers. No rigid criteria will be established other than the number of visits to the various medical facilities. Before the service member is actively entered into this pilot study, his records will be reviewed by the principal investigator to avoid entrance of an inappropriate subject. The aim of this selection process will be to discover twenty patients who have well documented histories of a greater than expected frequency of infection, either bacterial or viral in nature. After proper selection, the subjects will undergo the following immunologic studies.

- a. CBC (total white count and differential).
- b. Total serum immunoglobulins (G) (A) (M) (D) (E)
- c. Primary and secondary antibody responses will be measured.
- d. Absolute lymphocyte counts, B and T lymphocyte differentiation by rosetting, and surface immunofluorescent techniques will be accomplished. Functional lymphocyte activity will be determined by response to a lectin, such as PHA; and to an antigen, such as SKSD or candida albicans. The supernatant of the stimulated culture will be examined for development of lymphokine

activity by evaluation of migration inhibition factor activity. Monocytes/macrophages and polymorphonuclear leukocytes will be evaluated by NBT testing, by chemiluminescence, and by chemotactic ability.

e. In vivo testing will consist of delayed hypersensitivity skin testing performed to a battery of the following antigens:

- (1) Streptokinase
- (2) Streptodornase
- (3) Tetanus toxoid
- (4) C. candida albicans
- (5) PPD
- (6) Trichophyton
- (7) Phytohemagglutinins

All testing results will be compared with normal controls in the laboratory. The results will be evaluated in this light to determine if this type of immune evaluation is able to discriminate between the subject group and usual normal controls.

Progress:

None.

# Detail Summary Sheet

Date: 1 Oct 82      Prot No: 81/10      Status: Ongoing  
 Title:

An Evaluation of the Effects of Beta II Adrenergic Agents on Human Immunoglobulins and Antibody Response

Start Date:      Est Comp Date:  
 Principal Investigator:      Facility:

LTC L.E. Mansfield, MC

Dept/Sec: Allergy Clinic      Assoc Investigators  
 Key Words:  
 Beta II agonists; Immunoglobulins      LTC S. Smith, MC  
    LTC M.W. Johnson, MC  
    CPT I. Weissman, MC

Accumulative MEDCASE      Est      Periodic  
 Cost      OMA Cost:      Review Results  
 Study Objective:

To determine if the administration of Beta II adrenergic agents affect immunoglobulin levels and the ability to form specific antibodies in the primary and secondary immune response.

## Technical Approach:

Forty patients will be selected at random from the Pulmonary Clinic on the basis of a routine therapeutic decision. The physician in charge of their case will judge oral beta II adrenergic agents necessary to improve the patient's clinical pulmonary status. Prior to initiating this therapy, the patients will be told the nature of the study and its importance. The patients will have a blood sample drawn which will be used for analysis. Patients will begin on the appropriate oral beta II adrenergic agent and will return to clinic in one month and have a second specimen of blood obtained.

In those patients in whom it is deemed medically advisable, an influenzal and pneumococcal vaccine immunization will be given. These immunizations will be given only to those patients who may be reasonably expected to benefit from their use. A documented history of previous influenzal immunization will be obtained. The results will be analyzed by comparison of the pre-therapy and post-therapy levels of immunoglobulins. The effects on the expected rise of titer of the secondary antibody response will be compared to normal standards. The titer and presence of the primary antibody response



will be compared to reported standards. The serum specimens collected at both times will be analyzed for the following serum immunoglobulins: IgG, A, M, D and E. In all patients, whether or not they receive immunizations, influenzal and pneumococcal antibody titers will be determined on the pre-therapy and one-month specimens.

**Progress:**

Fifteen patients have been entered. The response appears to confirm the hypothesis. Additional patients will be entered.

Detail Summary Sheet

Date: 1 Oct 82      Prot No: 81/11      Status: Completed  
Title:

Clinical Evaluation of Tc99m-PIPIDA-Tin as a Hepatobiliary Agent

Start Date:      Est Comp Date:  
Principal Investigator:      Facility:

LTC T.J. Brown, MC

Dept/Sec:      Nuclear Medicine      Assoc Investigators  
Key Words:

Hepatobiliary scanning

Accumulative MEDCASE      Est      Periodic  
Cost      OMA Cost:      Review Results  
Study Objective:

Evaluate the safety and efficacy of Technetium Tc99m PIPIDA-Tin as a hepato-biliary agent.

Technical Approach:

Patients will be 18 years or over, nonpregnant females, non-breast feeding.

Clinical Indications: Patients with history of malignancy to assess metastases or define extent of metastases. Patients with no history of malignancy in whom malignancy is suspected. Liver function determination. Jaundice evaluation. Biliary tract obstruction. Evaluation of acute or chronic cholecystitis. Patients with other medical conditions that, in the investigator's opinion, suggest radioisotope hepato-biliary studies would be useful.

Evaluation of Scan Image: Evaluation of the image quality should be based on the following standards: Good quality image, diagnostically useful - acceptable.

Poor image quality, diagnostically not useful - unacceptable.

Criteria by which efficacy will be evaluated: Comparison with radiographic findings when indicated and available. Correlation with surgery, biopsy, and autopsy findings when available.

Utility of the study: Initial clinical impression should be compared with the final or clinical diagnosis and the utility of the procedure assessed.

Progress:

Annual review of this protocol was conducted in Sept 82. Ninety-one patients were entered in FY82. No adverse effects were noted. Appropriate consent was verified. FDA has now approved this agent for clinical use.

Detail Summary Sheet

Date: 1 Oct 82 Prot No: 81/12 Status: Ongoing  
Title:

A Novel Method of Hyposensitization Therapy with Russian Thistle Antigen

Start Date: Est Comp Date:  
Principal Investigator: Facility:

LTC L.E. Mansfield, MC

Dept/Sec: Allergy Clinic Assoc Investigators  
Key Words:

Hyposensitization; Russian thistle antigen

Accumulative MEDCASE Est Periodic  
Cost OMA Cost: Review Results

Study Objective:

To determine if oral administration of Russian Thistle pollen in a pharmacologically modified release form will be capable of: (a) Demonstrating immunologic changes that are comparable to standard parenteral allergen immunotherapy. (b) Demonstrating in a physiologic test, such as nasal provocation, evidence of lessened reactivity to allergen.

Technical Approach:

Thirty adult allergic patients, who are significantly sensitive to Russian Thistle allergen by history and skin testing, will be the subjects for this protocol. The nature and purpose of this study will be explained to them. The study will be conducted from December to March, when ambient Russian Thistle pollen is not present in El Paso.

The subjects will report to the Allergy Clinic. Prior to the initiation of therapy, the subjects will have:

- a. Titrated prick-puncture skin tests performed (3mm wheal end point).
- b. 5 ml blood taken to measure specific serum IgG, IgM and IgE antibodies to Russian Thistle allergen.
- c. Nasal sensitivity to Russian Thistle allergen determined by nasal provocation (doubling of nasal airway resistance as end point).

The patients will be given capsules containing specifically prepared Russian Thistle allergen. This material will be lacquered to avoid digestion and dissolution in the acid media of the stomach. The schedule on a daily basis: 0.15, 0.30, 0.60, 0.90, 1.20, 1.60, 1.90, 2.0, 2.5, 3.0, 4.0, 5.0, 7.0, 9.0, 12.0, 15.0, 20.0, 25.0, 30.0, 40.0, 50.0 mg.

50 mg will be given weekly as a maintenance dose for four more weeks. After this total schedule, the measurements made prior to therapy will be repeated. The results will be analyzed by paired "t" testing of the mean responses.

Progress:

This study has not been activated pending availability of resources.

# Detail Summary Sheet

Date: 1 Oct 82      Prot No: 81/13      Status: Completed  
 Title:

Effect of Streptokinase on the Sinoatrial Node, the Atrioventricular Node, and the Myocardium of the Canine Heart

Start Date:      Est Comp Date:  
 Principal Investigator:      Facility:

CPT R.D. Latham, M.D.  
 Dept/Sec: Dept Medicine      Assoc Investigators  
 Key Words:

Streptokinase; Sinoatrial node; Atrioventricular node

Accumulative MEDCASE	Est	Periodic
Cost	OMA Cost:	Review Results

Study Objective:

Determine if the systemic effects of streptokinase are evident when the drug is administered by intracoronary technique and the effect if any of streptokinase on the SA, AV nodes or myocardium.

## Technical Approach:

Approximately ten mongrel dogs will be weighed and anesthetized with pentobarbital using 30 mg/kg dose. The animal will then be intubated with an endotracheal tube and ventilated with approximately 225 cc TV and rate of 14-16 with monitoring of ABC's. A surface lead EKG lead II will be placed. The dogs will be heparinized with dose of 2 mg/kg. Central aortic pressure will be monitored via a catheter placed from the carotid. A median sternal splitting incision will be performed, the heart exposed and cradled in the pericardium. Student's paired t-test will be used to determine the significance between similar observed and control variables. Grouping will be optional depending on initial results.

## Progress:

The control trials revealed no change in C.O. or mean blood pressure. The heart rate varied from a range of 60-130 beats per minute with no change in individual trials. The mean cardiac output was 2.2 L/min, mean systolic pressure 99 mm/Hg and mean heart rate 95 beats/min.

The intracoronary infusion group had a cardiac output range 1.5-2.5 L/min. Mean arterial blood pressure range was 73 to 130. The mean cardiac output was 2.14 L/min, mean systolic pressure was 99 mm/Hg and mean post-perfusion heart rate was 98 beats/min. There was no significant change in pre- and post-infusion values.

The more important trial involved the direct perfusion of the sinus node with ECG monitoring. The heart rate was continuously monitored and recorded at five minute intervals. There was no significant difference in individual trials.

The hearts were submitted to pathology for morphologic analysis. No significant pathologic changes were observed in the sinus node and myocardium of saline control vs streptokinase models.

In summary, seven mongrel dogs underwent selective cannulation and perfusion of the sinus nodal artery with streptokinase. Two mongrel dogs underwent systemic perfusion. There was no significant change in heart rate or hemodynamic parameters noted during perfusion of the sinus nodal artery. Systemic perfusion via peripheral IV also produced no significant change in cardiac output, blood pressure, total systemic resistance, or heart rate for the time perfused.

Detail Summary Sheet

Date: 1 Oct 82      Prot No: 81/17      Status: Terminated

Title:

SWOG 7984: The Treatment of Chronic Stage CML with Pulse,  
Intermittent Busulfan Therapy with or without Oral Vitamin-A, Phase  
III

Start Date:

Est Comp Date:

Principal Investigator:

Facility:

LTC P.C. Farley, MC

Dept/Sec: Dept Medicine, Oncology

Assoc Investigators

Key Words:

Leukemia

Accumulative MEDCASE

Est

Periodic

Cost

OMA Cost:

Review Results

Study Objective:

To determine the efficacy of standard pulse, intermittent busulfan  
therapy plus oral vitamin A in prolonging the chronic phase of CML,  
and hence in prolonging survival.

Technical Approach:

The details are lengthy and specified in the original SWOG  
protocol. Duplicates are kept on file in the Dept Clinical  
Investigation, WBAMC, and are available upon request.

Progress:

See Unit Summary.



Detail Summary Sheet

Date: 1 Oct 82      Prot No: 81/18      Status: Terminated

Title:

SWOG 8001: Evaluation of Two Maintenance Regimens in the Treatment of Acute Lymphoblastic Leukemia in Adults, Phase III

Start Date:

Est Comp Date:

Principal Investigator:

Facility:

LTC P.C. Farley, MC

Dept/Sec: Dept Medicine, Oncology

Assoc Investigators

Key Words:

Leukemia

Accumulative MEDCASE

Est

Periodic

Cost

OMA Cost:

Review Results

Study Objective:

1. To evaluate the effectiveness, as determined by the complete remission-rate, of the L10 protocol using Vincristine, Prednisone, and Adriamycin for induction, followed by intensive consolidation in the treatment of adult ALL in a group-wide study.

2. To compare the effect on remission duration and survival of two maintenance regimens: The L10 "eradication" regimen vs. cyclic therapy with POMP-COAP-OPAL.

3. To determine the reproducibility of the FAB histologic classification and correlation of response to therapy of ALL in adults.

Technical Approach:

The details are lengthy and specified in the original SWOG protocol. Duplicates are kept on file in the Dept Clinical Investigation, WBAMC, and are available upon request.

Progress:

See Unit Summary.

# Detail Summary Sheet

Date: 1 Oct 82 Prot No: 81/19 Status: Terminated

## Title:

SWOG 8006: Preoperative Reductive Chemotherapy for Stage III or IV Operable Epidermoid Carcinoma of the Oral Cavity, Oropharynx, or Larynx, Phase III

Start Date:

Est Comp Date:

Principal Investigator:

Facility:

LTC P.C. Farley, MC

Dept/Sec: Dept Medicine, Oncology

Assoc Investigators

Key Words:

Carcinoma, larynx; Carcinoma, pharynx

Accumulative MEDCASE  
Cost

Est  
OMA Cost:

Periodic  
Review Results

Study Objective:

The purpose of this study is to determine the length of remission, recurrence-rates, survival-rates, and pattern of recurrence for patients receiving therapy utilizing surgery and post-operative radiation vs. combined therapy utilizing pre-operative radiation vs. combined therapy utilizing pre-operative chemotherapy, surgery and post-operative radiation therapy in operable Stage III or IV epidermoid carcinoma of the head and neck.

Technical Approach:

The details are lengthy and specified in the original SWOG protocol. Duplicates are kept on file in the Dept Clinical Investigation, WBAMC, and are available upon request.

Progress:

See Unit Summary.

Detail Summary Sheet

Date: 1 Oct 82 Prot No: 81/20 Status: Terminated

Title:

SWOC 8014: Colchicine in Refractory Chronic Lymphocytic Leukemia,  
Phase I-II

Start Date:

Est Comp Date:

Principal Investigator:

Facility:

LTC P.C. Farley, MC

Dept/Sec: Dept Medicine, Oncology

Assoc Investigators

Key Words:

Leukemia; Colchicine

Accumulative MEDCARE

Est

Periodic

Cost

OMA Cost:

Review Results

Study Objective:

1. To determine the maximum dose of colchicine that may safely be administered on a once weekly basis.
2. To determine the response rate (standard error +/- ten percent) in patients with chronic lymphocytic leukemia.
3. To determine quantitative and qualitative toxicity of the drug colchicine administered on a once weekly schedule.

Technical Approach:

The details are lengthy and specified in the original SWOC protocol. Duplicates are kept on file in the Dept Clinical Investigation, WBAMC, and are available upon request.

Progress:

See Unit Summary.

Detail Summary Sheet

Date: 1 Oct 82 Prot No: 81/21 Status: Terminated

Title:

SWOG 8012: Treatment for Advanced Adenocarcinoma and Large Cell Carcinoma of the Lung: FOMi vs CPA vs FOMi/CAP, Phase III

Start Date:

Est Comp Date:

Principal Investigator:

Facility:

LTC P.C. Farley, MC

Dept/Sec: Dept Medicine, Oncology

Assoc Investigators

Key Words:

Carcinoma, lung

Accumulative MEDCASE

Est

Periodic

Cost

OMA Cost:

Review Results

Study Objective:

1. To evaluate by pairwise comparison the response-rate, duration of response and survival of 3 regimens FOMi, CPA and FOMi/CAP in patients with advanced (TMN Stage III M1) adenocarcinoma and large cell undifferentiated carcinoma of the lung.
2. To evaluate the degree of non-cross resistance of FOMi in CAP failures and of CAP on FOMi failures.
3. To compare the toxicities and side effects of FOMi and CAP.

Technical Approach:

The details are lengthy and specified in the original SWOG protocol. Duplicates are kept on file in the Dept Clinical Investigation, WBAMC, and are available upon request.

Progress:

See Unit Summary

# Detail Summary Sheet

Date: 1 Oct 82      Prot No: 81/22      Status: Terminated

## Title:

SWOG 8015: Evaluation of Two Combination Chemotherapy Programs, Adriamycin and Cis-Platinum (AP) versus Adriamycin, Cis-Platinum plus VP 16 (VAP), in the Treatment of Extensive Squamous Cell Carcinoma of the Lung, Phase III

Start Date:

Est Comp Date:

Principal Investigator:

Facility:

LTC P.C. Farley, MC

Dept/Sec: Dept Medicine, Oncology      Assoc Investigators

Key Words:

Carcinoma, lung

Accumulative MEDCASE

Est

Periodic

Cost

OMA Cost:

Review Results

Study Objective:

1. To determine the activity, in terms of response rate, remission duration, and survival in patients with extensive squamous cell (epidermoid) carcinoma of the lung, for two combination chemotherapy programs; adriamycin and Cis-Platinum (AP) versus VP 16-213, Adriamycin and Cis-platinum (VAP).
2. To evaluate the relative toxicities of these respective regimens.
3. To assess the feasibility and reliance of applying "measurable versus evaluable" criteria of tumor regression in determining therapeutical response.
4. To correlate tumor grade with response and survival.

Technical Approach:

The details are lengthy and specified in the original SWOG protocol. Duplicates are kept on file in the Dept Clinical Investigation, WBAMC, and are available upon request.

Progress:

See Unit Summary.

Detail Summary Sheet

Date: 1 Oct 82 Prot No: 81/23 Status: Terminated

Title:

SWOG 8027: The Natural History of Pathological Stage T<sub>1-2</sub> N<sub>0</sub>  
M<sub>0</sub> ER + Breast Cancer, Phase III

Start Date:

Est Comp Date:

Principal Investigator:

Facility:

LTC P.C. Farley, MC

Dept/Sec: Dept Medicine, Oncology

Assoc Investigators

Key Words:

Carcinoma, breast

Accumulative MEDCASE  
Cost

Est  
OMA Cost: \$1898(1898)

Periodic  
Review Results

Study Objective:

To document recurrence rates, patterns of recurrence, and survival among patients with Stage I or Stage II node negative (T<sub>1-2</sub> N<sub>0</sub> M<sub>0</sub>) breast cancer whose tumors are determined to be estrogen receptor positive at the time of surgery.

Technical Approach:

The details are lengthy and specified in the original SWOG protocol. Duplicates are kept on file in the Dept Clinical Investigation, WBAMC, and are available upon request.

Progress:

See Unit Summary

# Detail Summary Sheet

Date: 1 Oct 82 Prot No: 81/24 Status: Terminated

## Title:

The Re-Use of Hollow Fiber Hemodialyzer, a Randomized Trial

Start Date:

Est Comp Date:

Principal Investigator:

Facility:

MAJ M. Siedlecki, MC

Dept/Sec: Dept Medicine, Renal Cl

Assoc Investigators

Key Words:

Hemodialysis

Accumulative MEDCASE

Est

Periodic

Cost

OMA Cost:

Review Results

Study Objective:

A double blind, randomized cross-over study of the effect of hollow fiber artificial kidney re-use on chronic hemodialysis patients.

Technical Approach:

In a double blind fashion, 2 groups, new and re-used group, 5 patients each will be treated concurrently with new and re-used hemodialyzers. In the re-used group each patient will be treated with the same "own" kidney; the kidneys will not be mixed. The hemodialysis procedure will not be changed in any way from the way it is practiced now. The rinsed hemodialysers will be used six times and after clearance determinations, done during the 6th re-use, discarded.

Progress:

The principal investigator was reassigned. No progress was reported.

# Detail Summary Sheet

Date: 1 Oct 82 Prot No: 81/28 Status: Terminated

Title:

The Effects of Erythromycin Treatment on Neutrophil Chemotaxis

Start Date:

Est Comp Date:

Principal Investigator:

Facility:

LTC L.E. Mansfield, MC

Dept/Sec: Dept Medicine, Allergy Cl

Assoc Investigators

Key Words:

Chemotaxis; erythromycin

Accumulative MEDCASE

Est

Periodic

Cost

OMA Cost:

Review Results

Study Objective:

To determine if in vivo treatment with erythromycin leads to an improvement in neutrophil chemotaxis in vitro.

Technical Approach:

Twenty adult patients with severe atopic dermatitis will be selected from patients attending the Dermatology Clinic. The nature and purpose of the study will be explained to them. Diagnostic criteria for atopic dermatitis will be the usual clinical criteria for atopic dermatitis to include: (1) Family history of atopy. (2) characteristic distributions of lesion. (3) white dermatographism. (4) characteristic scaly lichenified, or nummular appearance. (5) Elevated serum IgE level. (6) No evidence of contact dermatitis. (7) Biopsy compatible with atopic dermatitis. The skin manifestations must be present, along with two or three other characteristics. The twenty patients will have atopic dermatitis that has not responded to topical corticosteroids. They will be divided randomly into two groups, one to receive erythromycin, 250mg, QID; one to receive 10mg prednisone TID for five days, and 30mg QOD in a.m. for five further doses. A third group of 10 patients treated only with Eucerin and antihistamines of the H<sub>1</sub> class will be studied as controls. Blood samples will be obtained just prior to beginning and at the end of the medication course. These samples will be used to provide white cells (polymorphonuclear leukocytes) for chemotaxis in a modified Boyden Chamber technique, and an agarose technique. Random



migration and the response to various chemoattractants will be measured. The results of the pre-therapy and post-therapy specimens will be compared. The differences in changes between groups will also be compared and if the results suggest an effect from the erythromycin beyond the effect from the prednisone, the study will be expanded.

Progress:

None.

Detail Summary Sheet

Date: 1 Oct 82 Prot No: 81/29 Status: Terminated

Title:

The Effect of a Lipxygenase Inhibitor on Phytohemagglutinin Stimulated Lymphocyte Blastogenesis in Rheumatoid Arthritis.

Start Date:

Est Comp Date:

Principal Investigator:

Facility:

LTC L.E. Mansfield, MC

Dept/Sec: Dept Medicine, Allergy Cl

Assoc Investigators

Key Words:

Lipxygenase; Rheumatoid arthritis; lymphocyte stimulation

Accumulative MEDCASE

Est

Periodic

Cost

OMA Cost: \$1065(1065)

Review Results

Study Objective:

To determine effects of a lipxygenase inhibitor on lymphoblastogenesis in patients with rheumatoid arthritis.

Technical Approach:

Ten patients with active rheumatoid arthritis will be chosen from the Rheumatology Clinic. Five normal volunteers will be selected from among the physician staff of WBAMC. Thirty milliliters of blood will be drawn from each subject and lymphocytes separated for microtechnique phytohemagglutinin lymphocyte stimulation. The cultures will be done in the usual fashion and also with the addition of four concentrations of 5,8,11 eicosatrienoic acid ( $2 \times 10^{-7}$ ,  $10^{-6}$ ,  $10^{-5}$ ,  $10^{-4}$  molar). The response of the normal and rheumatoid cells to this compound, as contrasted to the usual cultures, will be compared.

Progress:

None.

Detail Summary Sheet

Date: 1 Oct 82 Prot No: 81/30 Status: Terminated

Title:

The Effects of a Histamine (H<sub>2</sub>) Antagonist on the Lupus-like Syndrome of New Zealand Mice

Start Date:

Est Comp Date:

Principal Investigator:

Facility:

LTC L.E. Mansfield, MC

Dept/Sec: Dept Medicine, Allergy Cl

Assoc Investigators

Key Words:

Cimetidine; Lupul erythromatosis

Accumulative MEDCASE

Est

Periodic

Cost

OMA Cost:

Review Results

Study Objective:

To determine if routine treatment with an H<sub>2</sub>-receptor antagonist will influence the time course or severity of the systemic lupus erythematosus-like syndrome of New Zealand mice.

Technical Approach:

One hundred fifty NZB/NZW female mice will be used for this experiment. At the beginning of the experiment they will be approximately one month of age. One-hundred mice will be the treatment group; 50 mice will be the sham group. Five out of seven days the treated mice will receive an injection of 100 mg/kg cimetidine. The control mice will receive an injection of vehicle. Beginning at three months of age, ten treated mice and five sham mice will be sacrificed. Blood will be obtained and analyzed for autoantibodies and immune complexes. The kidneys will be processed by florescent staining for immunoglobulins and complement. Any mouse that dies spontaneously will be counted in the appropriate group for that month and an attempt to utilize the kidney for immunofluorescence will be made.

Progress:

None

# Detail Summary Sheet

Date: 1 Oct 82 Prot No: 81/36 Status: Ongoing

## Title:

Phase II Studies on Ketoconazole (Keto) - Comparison of Two Different Doses of Keto in Treating Coccidiomycosis

Start Date:

Est Comp Date:

Principal Investigator:

Facility:

CPT Idelle Weismann, MC

Dept/Sec: Dept Medicine

Assoc Investigators

Key Words:

Coccidiomycosis; Ketoconazole

MAJ S. Smith, MC

Accumulative MEDCASE

Est

Periodic

Cost

OMA Cost:

Review Results

Study Objective:

To determine the most efficacious dose of Keto for humans with coccidioidomycosis. To evaluate the toxicity of Keto in humans with doses up to 1600 mg per day. To evaluate the CSF penetration of very high doses of Keto.

Technical Approach:

The details are lengthy and specified in the original protocol, which is on file in the Dept Clinical Investigation, WBAMC, and is available upon request.

Progress:

Annual review of this protocol was conducted in September 1982. Three of these patients were treated with doses of 400 mg/day or less. No adverse effects were noted in this group. An additional patient, while being treated with 80 mg/day, suffered a pulmonary embolus and died. This patient had disseminated coccidioidomycosis and had been diagnosed prior to terminal event as having had multiple small pulmonary emboli and accordingly she was receiving heparin at the time of her demise. There was no evidence clinically or at the time of autopsy that this pulmonary embolus was related to the ketoconazole. The principal investigator also informed the committee that no other investigators to this date have reported pulmonary embolus as a side effect or adverse reaction to the ketoconazole.

Detail Summary Sheet

Date: 1 Oct 82 Prot No: 81/38 Status: Ongoing

Title:

The Development of Subsensitvity to Atropine

Start Date:

Est Comp Date:

Principal Investigator:

Facility:

LTC L.E. Mansfield, MC

Dept/Sec: Dept Medicine, Allergy Cl

Assoc Investigators

Key Words:

Atropine; Asthma

Accumulative MEDCASE  
Cost

Est  
OMA Cost:

Periodic  
Review Results

Study Objective:

To determine if repeated use of atropine sulfate as a bronchodilator, by the inhalant routes, leads to development of subsensitvity.

Technical Approach:

Twenty adult asthmatic patients will be selected at random from the Pulmonary and Allergy Clinics at WBAMC. The nature and purpose of the study will be explained. On the first day of the experiment they will be tested at the Pulmonary Function Lab according to the following protocol:

- a. 24 hours without oral bronchodilators
- b. Baseline pulmonary functions consisting of conventional spirometry, flow volume loops, and plethysmography.
- c. Inhalation of atropine sulfate 2 mg by nebulizer.
- d. Repeat pulmonary function.

After this the patients will be instructed in the use of a home nebulizer. They will use atropine sulfate 2 mg by nebulizer three times a day for 14 days. At the end of the period, the patients will undergo the same testing as on the initial day. If there is a decrease in response, then ten subjects will be retested after inhalation of 0.5 mg atropine and ten after inhaling 1.0 mg atropine, in addition to the previous 2.0 mg.

Analysis will consist of t-testing of the mean response on each occasion. In the ten subjects of each incremental group, comparison will be made to ascertain which increment, if one is required, to restore responsiveness to the original testing level.

**Progress:**

Seven patients have been entered. The study will continue until 14-15 patients have completed the study.

# Detail Summary Sheet

Date: 1 Oct 82      Prot No: 81/39      Status: Ongoing

## Title:

The Usefulness of NonAcetylated Salicylates in the Treatment of Inflammatory Disease in Patients with Aspirin Idiosyncratic Asthma.

Start Date:

Est Comp Date:

Principal Investigator:

Facility:

LTC L.E. Mansfield, MC

Dept/Sec: Dept Medicine, Allergy Cl

Assoc Investigators

Key Words:

Salicylates; Asthma

Accumulative MEDCASE

Est

Periodic

Cost

OMA Cost:

Review Results

Study Objective:

To determine if non-acetylated salicylates can be used safely in the treatment of aspirin-idiosyncratic asthmatics with inflammatory disease.

Technical Approach:

Thirty patients with a history of aspirin idiosyncrasy will be selected from the Pulmonary and Allergy Clinics of WBAMC. The nature and purpose of the study will be explained to them. They will report to the Pulmonary Function Lab on four occasions. They will be tested according to following protocols. Measured pulmonary functions will be conventional spirometry and flow volume determinations on each occasion.

DAY 1	Day 2	Day 3	Day 4
<u>Placebo</u>	<u>Aspi in</u>	<u>Disalcid</u>	<u>Trisilate</u>
1 cap	32 mg	250 mg	250 mg
2 cap	64 mg	500 mg	500 mg
3 cap	128 mg	750 mg	750 mg
4 cap	325 mg	1000 mg	1000 mg

The patients will not take oral bronchodilators for 24 hours except for corticosteroids. They will be managed by inhaled bronchodilating agents. Each dose will be spaced 30 minutes apart. All medications will be given in identical opaque white capsules, and the patient will be blinded as to the contents of these capsules.

A significant test for each person will be a fall in one second forced expiratory volume greater than twenty percent of predicted FEV<sub>1</sub>, over the fall during the placebo challenge. Any patient who develops clinical symptoms will have their bronchoconstriction reversed. Any subject whose aspirin challenge is negative will be excluded from the study. Each testing will be compared to the placebo day, in terms of possible positive responses.

Specifically, patients will not be entered unless their FEV<sub>1</sub> is greater than eighty percent of predicted at the onset of the study, and patients who develop greater than a twenty percent fall in FEV<sub>1</sub> will be eliminated from the study at that point.

**Progress:**

Patient entry may commence in FY83 if resources permit.



Detail Summary Sheet

Date: 1 Oct 82      Prot No: 81/40      Status: Completed

Title:

The Useage of Beta 2 Agonist in Topical Treatment of Allergic Skin Reactions.

Start Date:

Est Comp Date:

Principal Investigator:

Facility:

LTC L.E. Mansfield, MC

Dept/Sec: Dept Medicine, Allergy Clinic      Assoc Investigators

Key Words:

Beta II agonist; Histamine; Eosinophil migration; Mast cells

Accumulative MEDCASE

Est

Periodic

Cost \$8,037

OMA Cost: \$825(825)

Review Results

Study Objective:

To determine whether locally applied B<sub>2</sub> agonist suppresses the histamine release, eosinophil migration response, and ultrastructural changes of mast cells in human allergic skin reactions.

Technical Approach:

Adult patients will be selected on the basis of a 4+ positive prick skin test to ragweed allergen from the Allergy Clinic. They will undergo skin blister provocation and skin biopsy and the resultant materials tested.

Progress:

Terbutaline applied topically to an allergen-challenged cutaneous skin test site significantly inhibited the reaction. Ultramicroscopic examination revealed inhibition of mast cell degranulation with topical terbutaline treatment. This material will be presented at the International Allergy and Immunology Meeting (London Oct 82) and a manuscript has been accepted for publication in the Journal of Allergy and Clinical Immunology.

# Detail Summary Sheet

Date: 1 Oct 82 Prot No: 81/45 Status: Completed

## Title:

The Effects of Chronic Bronchoconstriction on Bronchial Smooth Muscle and Bronchial Architecture

## Start Date:

## Est Comp Date:

Principal Investigator:

Facility:

LTC L.E. Mansfield, MC

Dept/Sec: Dept Medicine, Allergy Clinic

Assoc Investigators

## Key Words:

Bronchoconstriction

P.A. Miles, MD., DAC

B.E.F. Reimann, DSc, DAC

Accumulative MEDCASE

Est

Periodic

Cost

OMA Cost: \$911(1249)

Review Results

## Study Objective:

To determine if repeated bronchoconstriction caused by immunologic or chemical stimulus leads to the observed bronchial smooth muscle hypertrophy and the other changes noted in the pathological examination of the asthmatic lung.

## Technical Approach:

Weanling guinea pigs will be used for this study. They will be divided into four groups of ten animals each, according to the protocol below.

Group I: Saline challenge, no bronchoconstriction expected.

Group II: Will be challenged daily until wheezing with 48/80, 1 mg per ml, by inhalation.

Group III: Guinea pigs who have been sensitized to egg albumin, induced with pertussis vaccine, will comprise this group. They will undergo inhalation challenge with a 1:100 w/v egg albumin solution until wheezing.

Group IV: As in group III, with prior inhalation of 20 mg cromolyn, before being challenged with egg albumin.

This procedure will be carried out five days per week for a period of twelve weeks. This will approximate the time in a human life span from childhood until sexual maturity.

A lucite chamber will constrain the guinea pigs during respiratory function studies for aerosol administration. The end point of a challenge will be wheezing in a guinea pig, which can be heard audibly through a stethoscope and can be monitored by nasal and perioral cyanosis. At the completion of the study, each of the animals will be sacrificed and a wet and dry weight of the lung obtained. The pulmonary tissue will be submitted for routine histological examination. Specimens will be randomized and blinded.

The following data will be evaluated:

- a. Differences in the weight of the lung between the four groups.
- b. Microscopic examination of lung tissue containing bronchi, and a second examination containing bronchials. During this examination, thickness of the bronchial smooth muscle, the basement membrane, and any evidence of bronchial mucous gland hyperplasia will be evaluated.
- c. If there are any significant changes found under light microscopy, selected segments, which have been prepared from the control group, and the three challenge groups will be examined under electron microscopy. It would be hoped that this examination may provide further light on distortions of the bronchial architecture.

#### Progress:

As a pilot study guinea pigs were divided into three groups of four pigs each and exposed to an aerosol five days each week for nine weeks. Group I, the control group, received an aerosol of 0.01M PBS, pH-7.1. Group II received 50 mg/ml of the compound 48/80 in 0.01M PBS, pH-7.1. Group III was challenged with 0.1cc of 2 mg/ml ovalbumin and 0.1cc of 100 ug/ml pertussigen i.p. two weeks prior to beginning the aerosol treatment and were then exposed to 0.1 mg/ml of ovalbumin in 0.01M PBS, pH-7.1. Each guinea pig in Groups II and III was exposed each day to aerosol until it wheezed for approximately one minute (range of total exposure 2-20min/day). If severe wheezing continued after removal from the aerosol chamber, the guinea pig was given epinephrine until wheezing ceased. The control guinea pigs were exposed to PBS aerosol for an amount of time equal to that of the longest exposure time in either experimental group.

After nine weeks of exposure, the guinea pigs were killed and three sections of each lung stained with H&E and examined by light microscopy. The sections were examined for alveolar size, basement membrane thickening, thickening of the vascular walls, and smooth muscle hypertrophy. Although abnormalities were observed in several of the parameters, the two experimental groups could not be distinguished from the control group.

A new animal model, which has mucous secreting cells present, is being investigated to continue the study.

# Detail Summary Sheet

Date: 1 Oct 82 Prot No: 81/54 Status: Ongoing  
 Title:  
 High Resolution Electrophoretic Screening of Body Fluid Proteins

Start Date: Est Comp Date:  
 Principal Investigator: Facility:

CPT I.L. Levey, MC

Dept/Sec: Dept Medicine Assoc Investigators  
 Key Words:

Electrophoresis

Accumulative MEDCASE	Est	Periodic
Cost	OMA Cost: \$771(1854)	Review Results
Study Objective:		

Study the qualitative and quantitative patterns of proteins in human serum by high resolution two-dimensional electrophoresis. Proteins will be separated in the first dimension according to the net electrical charge of their constituent amino acids by the technique of isoelectric focusing, and in the second dimension according to their molecular weight by electrophoresis in the presence of sodium dodecyl sulfate. This technique can resolve, in theory as well as in practice, a thousand or more individual peptides. Under appropriate conditions, this technique can be expected to depict many of the individual protein components in human serum and other body fluids. If such resolution can be achieved, and a very large number of different peptides be seen, then variations related to disease may be studied, identifications made and the entities of greatest interest isolated.

While the spectrum of serum components in both health as well as disease is of interest, initial studies will be directed toward patients (1) with malignant disease (2) those undergoing chronic hemodialysis, (3) those with hepatic disease, and (4) those with inflammatory/autoimmune diseases.

## Technical Approach:

The major objective of the proposed research is to analyze the protein composition of human serum in health and disease. Four specific categories of patients have been selected for initial screening based upon either well-documented abnormalities of routine serum protein electrophoresis or their potential for protein abnormality. These categories include:

a. Patients with malignant disease, including plasma dyscrasias. Alterations of both beta and gamma globulins have been noted, as well as microheterogeneities of serum albumin. Patients will be studied before and during therapy, as well as during progression of disease.

b. Patients with protein-losing nephropathies and those undergoing hemodialysis. Many patients on hemodialysis develop protein electrophorograms resembling type 3 hyperlipoproteinemia. Additionally, those with collagen vascular diseases often experience remission of symptoms and occasionally alteration of serologic status following dialysis.

c. Patients with hepatic disease. The liver is the primary organ for synthesis of most plasma proteins other than the immunoglobulins. However, the Kupffer cells of the liver are involved with the immune system in that they process antigens absorbed from the gut. As a consequence, disorders involving the liver can result in abnormalities of virtually all of the plasma proteins.

d. Patients with inflammatory and/or autoimmune disease. Patients with rheumatic diseases frequently demonstrate plasma protein abnormalities, most commonly associated with the inflammatory response and those resulting from increased antigenic stimulation of the immune system.

Patients will be selected from those with documented abnormalities of routine serum protein electrophoresis as well as those encountered during routine ward activities.

#### Progress:

Four objectives have been realized: (1) Standardization of the electrophoretic technique; (2) development of a procedure for serum collection and purification to minimize hemoglobin contamination; (3) completion of preliminary experiments that suggest qualitative abnormalities in the protein composition of serum from patients with known adenocarcinoma; (4) familiarization of laboratory technicians with the experimental technique.

Problems and objectives remaining at this time include (1) determination of appropriate ampholyte pH for optimal resolution of serum proteins by isoelectric focusing. It now appears that a single ampholyte preparation, e.g. pH 3.5-10, may provide better separation than mixtures of ampholytes with different pH ranges. (2) Comparison of staining sensitivity achieved by coomassie brilliant blue R-250 with the recently-described silver staining technique (Oukley et al 1980; Merrell et al 1981). (3) Second-dimension SDS electrophoresis as longer slab gels to improve resolution. This problem has been discussed with the DCI staff and purchase of the BioRad Protein electrophoresis apparatus has been suggested.

Upon completion of the preliminary experiments the systematic analysis of serum collected from patients with known and unknown primary tumor sites will begin. Ideally, a laboratory technician could initially devote one-third to one-half time to this project and the PI will arrange to spend one-half day weekly in the performance and supervision of the investigation. It is notable that during the past three months two groups of investigators have described preliminary results from similar studies. Biochemists from the Rush Medical College, Chicago, IL, speaking at the Fourth Annual Symposium on Breast Cancer, San Antonio TX, used two-dimensional checkplaces to identify and stage patients with breast carcinoma. Secondly, Dr. Norman Anderson, of the Argonne National Laboratory, demonstrated computer analyses of two dimensional electroplerograms (JAMA 246:2620) and proposed the preparation of "protein indices" from human cells and fluids in health and disease as an aid to diagnosis. Clearly the prospects for studies such as those described are significant and merit intensive laboratory investigation.

# Detail Summary Sheet

Date: 1 Oct 82 Prot No: 81/56 Status: Ongoing

## Title:

Ticlopidine Hydrochloride - A Clinical Trial in Patients with Transient Cerebral or Monocular Ischemic Attacks

Start Date:

Est Comp Date:

Principal Investigator:

Facility:

COL M. Maccario, MC

Dept/Sec: Dept Medicine

Assoc Investigators

## Key Words:

Ticlopidine; cerebral ischemia

Accumulative MEDCASE

Est

Periodic

Cost

OMA Cost:

Review Results

## Study Objective:

To determine in a double-blind, randomized, parallel, controlled clinical trial whether ticlopidine hydrochloride can prevent the occurrence of transient or prolonged retinal or cerebral ischemic attacks (CIA), cerebral infarction (CI) as well as occlusive cardiovascular events in patients who are suffering from TIA or amaurosis fugax.

## Technical Approach:

Only nonsurgical candidates, or surgical candidates refusing surgical therapy, will be considered eligible for inclusion in this trial. Each qualified subject (to be verified by a neurologically qualified referee) will be randomly allocated to either ticlopidine hydrochloride or identical appearing control medication and in a double-blind fashion. Each participating center will have a separate randomization code for their institution and will essentially operate independent of other institutions enrolled in this trial. All data and case report forms generated by the participating centers will be forwarded to the central data processing center for inspection, handling, coding, correction, etc. Interim planned evaluations of accumulated data will be undertaken to monitor the safety and efficacy of the medications. Any proven or unacceptable side effects or toxicity due to therapy, or any obvious or sustained lack of efficacy of ticlopidine hydrochloride would be reason for premature termination of this clinical trial.

These properties of maintained prostacyclin production by the vessel wall and lack of platelet responsivity to prostaglandin endoperoxide stimulation in ticlopidine hydrochloride treated animals may be two very important therapeutic advantages of ticlopidine hydrochloride over ASA and the other non-steroidal anti-inflammatory compounds.

Ticlopidine hydrochloride at the dose of 250 mg BID for this therapeutic trial is well tolerated and safe in clinical tolerance and therapeutic studies conducted in the USA, Europe, and Japan. We anticipate no intolerance with the possible exception of infrequent, mild initial gastrointestinal discomfort in some patients. A more extensive description of ticlopidine hydrochloride is to be found in the drug monograph.

**Purpose of Trial:** The short term goal of this study is to investigate the effect of ticlopidine hydrochloride vs controlled therapy (ASA, or placebo) in preventing or reducing the incidence of CIA and/or amaurosis fugax attacks.

**Progress:**

This IND protocol is awaiting final approval by HSRRB.



# Detail Summary Sheet

Date: 1 Oct 82 Prot No: 81/57 Status:Terminated

## Title:

Late Incidence of Chronic and Occult Constrictive Pericardial Disease in Patients Treated by Radiotherapy for Hodgkins Disease

Start Date:

Est Comp Date:

Principal Investigator:

Facility:

COL M. Maccario, MC

Dept/Sec: Dept of Medicine

Assoc Investigators

Key Words:

Hodgkin's Disease; Radiotherapy; Pericarditis

Accumulative MEDCASE

Est

Periodic

Cost

OMA Cost:

Review Results

Study Objective:

To determine the incidence of pericardial disease in patients 24 months or greater post-radiotherapy for Hodgkin's Disease.

Technical Approach:

Thorough history and physical examination as well as blood studies, chest-x-ray and EKG will be performed. Ultrasound studies will be performed on the heart as well as MUGA scans to record the activity of the heart. Swan-Ganz cateterization will be performed in the Cardiac Cath Lab under the supervision of staff cardiologists, injecting novocaine at the elbow for anesthesia. With the aid of fluoroscopy, the catheter will be advanced through the heart into the arteries to the lungs. The catheter will allow measurement of pressures in the heart, requiring about 45-60 minutes.

Progress:

None

# Detail Summary Sheet

Date: 1 Oct 82 Prot No: 81/58 Status: Ongoing  
 Title:  
 The Prevalence of Antibiotic Tolerant Staphylococcus Aureus in  
 Nasal Cultures of Different Adult Population Group

Start Date: Est Comp Date:  
 Principal Investigator: Facility:

MAJ Frank J Baker, MC

Dept/Sec: Dept Medicine, Infect Dis Assoc Investigators  
 Key Words:

Staphylococcus

Accumulative MEDCASE	Est	Periodic
Cost	OMA Cost:	Review Results
Study Objective:		

To perform an epidemiological survey of Staphylococcus aureus tolerance from isolates not causing clinical infection and determine prevalence rates in different adult population groups.

## Technical Approach:

Three population groups consisting of 100 individuals in each group will be studied.

Normals consisting of two subpopulations. Young adults consisting of a defined population, i.e., active duty personnel billeted on post. Older adults consisting of a defined population, i.e., personnel in Health Services Command. This group would be composed of individuals free of chronic disease on no medication or antibiotic therapy.

Outpatients on antibiotics. Young adults from the Dermatology Acne Clinic. Older adults from the Pulmonary Clinic, patients with chronic obstructive pulmonary disease on cyclical antibiotic therapy.

Population with a high prevalence of staph nasal carriage. Renal dialysis and insulin dependent diabetic patients. Hospital personnel. Nasal swabs with culturettes will be obtained from each individual.

(1) All nasal swabs will be streaked on sheep blood agar (SBA). Identification of staph aureus will be by standard methods as per the Manual of Clinical Microbiology, i.e., colonial morphology gram stain.

(2) MIC will be performed in duplicate by standard methods as per the Manual of Clinical Microbiology. After primary inoculation and identification of an organism as staph aureus:

(a) A log phase, four hour growth of the organism will be prepared in Mueller-Hinton Broth (MHB). The inoculum will be standardized to a 0.5 McFarland and a 1/200 dilution prepared. Colony counts will be performed on each inoculum with a desired final concentration 1 or  $2 \times 10^5$  organisms/ml

Conclusions: If the prevalence rates were significantly different among the study population groups, the contribution of various epidemiological factors could be determined. If the prevalence rates of tolerant organisms were less than those causing clinical infection, the question of increased virulence and microbiological change of the organism from a colonizer to an invasive form would be raised. Conversely, if the prevalence was equal to or greater than those causing clinical infection, the clinical importance might be lessened for this phenomenon.

If in subsequent studies tolerance was found to be therapeutically important, i.e., necessitating higher dosages or different antibiotics not standardly used for staphylococcal infections, this prior identification of epidemiologic factors might aid in initial selection pending further characterization of the organism. By having identified those individuals with high prevalence rates of tolerant organisms and at increased risks for clinical infections with those organisms empiric selection of treatment might be facilitated.

Progress:

Personnel constraints have precluded activation of this protocol to date.

# Detail Summary Sheet

Date: 1 Oct 82 Prot No: 81/64 Status: Completed

## Title:

A Comparison of Streptokinase/Streptodornase (SK/SD) with Streptokinase (SK) alone in Delayed Hypersensitivity Skin Testing of Children Ages 5-17.

Start Date:

Est Comp Date:

Principal Investigator:

Facility:

LTC L.E. Mansfield, MC

Dept/Sec: Dept Medicine, Allergy Cl

Assoc Investigators

## Key Words:

Streptokinase; Streptodornase; Delayed hypersensitivity

Accumulative MEDCASE  
Cost

Est  
OMA Cost:

Periodic  
Review Results

## Study Objective:

To determine if streptokinase alone can replace streptokinase/streptodornase in the in vivo evaluation of cell mediated immunity by delayed hypersensitivity skin testing in children. To also evaluate the effects of acute minor illness on these skin tests.

## Technical Approach:

One hundred normal children, ages 5-17 years, approximately 50 females and 50 males, attending the Pediatric Clinic for routine school physicals, will be entered in a sequential order. They will be free of illnesses. The nature and purpose of this study and its possible risks will be explained to them and their parent(s). Two skin test sites will be selected, one on the right volar aspect of the forearm, the second in a similar location on the left forearm. SK/SD and SK sites will be alternated from left to right in an even/odd rotating sequence. The children will receive 0.1 ml of extract containing 100 u SK/25u SD intradermally in one site and 0.1 ml extract containing 100u SK intradermally in the second site.

A second study group will consist of children 5-17 years of age attending the Pediatric Clinic for minor infectious illness, usually upper respiratory infection.

The tests will be read at 24 and 48 hours. A positive response will be 5mm or greater of induration. However, all responses will be measured and recorded.

The results will be analyzed by nonparametric (Wilcoxon's signed rank test) and parametric (paired t-testing) analysis. The frequency of positive tests in the non-ill and ill groups will be compared by t-testing and the fifty percent probability test. Other evaluations will be performed as deemed appropriate by the statistical consultant.

#### Progress:

The antigen combination streptokinase/streptodornase (SK/SD) has been one of the most common recall antigens utilized in delayed hypersensitivity (D.H.) skin testing. However, this product is no longer commercially available. Streptokinase (SK), alone is still marketed. In this present study, the possible replacement of SK/SD with SK in D.H. skin testing was evaluated. Using ten normal healthy volunteers, it was established that 375U SK was comparable to 100U SK/25U SD in reaction. The response to these two reagents was compared in 200 hospital patients for whom DH skin testing was clinically indicated. Positive tests to SK/SD and SK occurred in 30 of 200 subjects. Reactions to SK/SD alone was found in 26 additional patients for a total of 56 positives. Reactions to SK alone were only 2, for a total of 32. These results suggest that at the concentrations used, SK is not suitable to replace SK/SD in DH testing and that SD represents the more potent streptococcal recall antigen in the combination.

Detail Summary Sheet

Date: 1 Oct 82      Prot No: 81/65      Status: Ongoing  
Title:  
Utility of Furosemide in Early Oliguric Renal Failure. Part of a  
Multi-center study.

Start Date:      Est Comp Date:  
Principal Investigator:      Facility:

MAJ S.F. Gouge, MC

Dept/Sec:      Dept Medicine      Assoc Investigators  
Key Words:

Furosemide; Renal failure

Accumulative MEDCASE      Est      Periodic  
Cost      OMA Cost:      Review Results

Study Objective:

A randomized study of furosemide effect on the outcome of oliguric acute renal failure. Can this diuretic convert a patient with oliguric acute renal failure to non-oliguric acute renal failure

Technical Approach:

Patients with renal oliguria will be considered for this study. Non-oliguric patients will also be included. However, the patients should not have post-renal obstruction, and if obstruction is suspected on clinical grounds, a complete workup will be done. In addition, pre-renal factors contributing to the renal failure, such as hypotension, volume depletion and congestive heart failure, will be corrected. Any patient with diminished hearing as determined clinically by questioning will be excluded from the study. Also any patient that experiences transient hearing loss after the first furosemide dose will be excluded from subsequent doses. Absence of administration of furosemide or other diuretic agents within the previous twelve hours will be a criteria for entry as will serum creatinine greater than 2.0 mg/dl.

There will be two patient groups, furosemide and saline placebo, as determined by the use of a random numbers table. Consecutive patients assigned an even number from the random numbers table will receive furosemide. Patients assigned an odd number will receive saline. The random numbers table will be employed by using horizontal rows.

Progress:

Patient entry has been infrequent. A new principal investigator, MAJ A. Henry, MC, will assume this protocol in FY83.

# Detail Summary Sheet

Date: 1 Oct 82      Prot No: 82/01      Status: Ongoing

Title:

Comparison of Modalities for Treatment of SLE Nephritis

Start Date:

Est Comp Date:

Principal Investigator:

Facility:

MAJ M. Nelson, MC

Dept/Sec:

Assoc Investigators

Key Words:

SLE nephritis

Accumulative MEDCASE

Est

Periodic

Cost

OMA Cost:

Review Results

Study Objective:

To evaluate the efficacy and side effects of single daily dose corticosteroids vs split dose steroid therapy. Provide an alternative form of therapy in patients with SLE Nephritis who have not responded to conventional steroids and to evaluate patients' clinical and serologic response to therapy

Technical Approach:

There will be two phases to the protocol with two arms in each phase. Patient selection: All patients above age 12, eligible for care at Army hospitals, with SLE diffuse proliferative nephritis, will be eligible for the study. We hope to have 25-30 patients in three years.

PHASE I: Patients will be randomized to the following therapy:

ARM 1. Single daily a.m. dose of prednisone 1 mg/kg (e.g. 60 mg q.d.)

ARM 2. One mg/kg/day of prednisone in four equal and divided doses every six hours (e.g. 15 mg of Prednisone q 6 hour)

Patients will continue on the above regimen for a minimum of one month. The patient's kidney function will be re-evaluated at the end of this initial treatment interval, and if there is:

a. A decrease in glomerular filtration rate (GFR) of greater than 25%;

b. A decrease in glomerular filtration rate of less than 25%, but with continued active urinary sediment and heavy proteinuria (greater than 3.5 grams/24 hours);

c. No significant change in the GFR, but remaining at a value less than 30% of normal (serum creatinine greater than 3.0 mg/dl).

Steroid dose would then be doubled (2 mg/kg/day) and continued for a minimum of two weeks, preferably four weeks. If any patient, after two to four weeks of therapy at 2 mg/kg/day (total of 6-8 weeks of steroid therapy) have:

a. Decrease in GFR of greater than 25%\*; or

b. Decrease in GFR of less than 25%, but with continued active urinary sediment and heavy proteinuria; or

c. Stabilization of glomerular filtration rate, but at a level less than 30% of normal (serum creatinine greater than 3.0), they would be declared steroid nonresponders and entered into Phase II of the protocol.

\*Baseline GFR is that clearance immediately prior to initiation or change in therapy.

Patients would be considered steroid responders if the glomerular filtration rate normalized (Normal GFR - Greater than 90cc/min, creatinine less than 1.8 mg% or 65 cc/min/m<sup>2</sup>), increased by greater than 50%, or remained stable with serum creatinine values of less than 3.0 mg/dl. Patients will also be considered as responders if their GFR decreases, but less than 25%, and the serum creatinine value is less than 3.0 mg/dl, and there is a clear and consistent improvement in the urinary sediment and the urine protein excretion. These patients should have their steroid dosages continued (e.g. 8-12 weeks), and the dosage thereafter very gradually tapered.

PHASE II: Patients will be randomized to the following therapy:

ARM 1: Pulse solumedrol therapy

ARM 2: Chlorambucil therapy

Pulse therapy would consist of 1 gram of intravenous bolus solumedrol therapy on three consecutive days with a subsequent continuation of steroids at 1 mg/kg/day, given as a split or single dose as on their previous schedule.

Chlorambucil would be administered as follows:



Start at dose of 2 mg/day and continue steroid therapy at 1 mg/kg/day. Chlorambucil dose should be increased by 2 mg increments every two weeks until

- a. There is distinct improvement in urinary sediment and GFR
- b. White count falls below 4500 or platelet below 100,000
- c. The daily dose reaches 10 mg/day.

In acutely ill patients with rapidly deteriorating renal function, chlorambucil may be initiated at a dose of 10 mg/day for 2-4 weeks and then tapered to a maintenance dose of 2-5 mg/day. Therapy should be continued until:

a. GFR normalizes, or improves by at least 50% for two consecutive months, with minimal urinary sediment and minimal proteinuria. At this time chlorambucil can be tapered at 2 mg/month and steroid slowly tapered. If patient has a flare of renal disease during chlorambucil taper, dose would be increased to the lowest dose that achieved remission with an attempt to taper and discontinue as above after remission is again obtained. Some patients could require long-term immunosuppressive therapy;

b. Four consecutive months of therapy that show no clear evidence of benefit to GFR, urinary sediment, or proteinuria;

c. GFR deteriorates by 50% from GFR at initiation of therapy;

To enter protocol, patient must:

a. Fulfill ARA criteria for SLE.

b. Have biopsy proven diffuse proliferative glomerulonephritis (DPGN) with active urine sediment and proteinuria. Patients must have never been on more than 0.5 mg/kg/day of prednisone or cytotoxic drugs prior to entering Phase I of the protocol. To enter Phase I patient must have had the diagnosis of DPGN nephritis for less than three months. Patients could be eligible for Phase II of the protocol without entering Phase I, if they had previously been on 1 mg/kg/day for one month and 2 mg/kg/day for 2-4 weeks and still have active disease.

c. On entering the protocol, patient must have CBC with differential and platelet count, SMA 20, urinalysis, 24-hour urine for creatinine clearance and protein, DNA% binding, C3, C4, CH50, ESR, FANA. At WBAMC Clinic immune complexes will be done.

d. After initiation therapy, patient must have creatinine, BUN, urinalysis, CBC, DNA% binding, C3, C4, and 24-hour urine for creatinine clearance three days post-therapy, one week post-therapy, and then once weekly for one month. If patient has stabilized, the

above data can then be obtained on a monthly basis. If patients therapy changes by either doubling dose of steroid or entering Phase II of protocol, patient should again have the above data obtained at three days, one week, and weekly times one month, and then on an every month basis.

e. Patient should be seen by physician when laboratory data is being obtained and fill in appropriate flow sheet on clinical signs and symptoms, laboratory and side effects of therapy. Flow sheets will be provided for this data gathering.

f. Consent form must be obtained and physician must counsel patient concerning the randomization of therapy, steroid side effect, and if pertinent, chlorambucil side effects to include possible complication of aplastic anemia, sterility, increased risk of malignancy, and increased susceptibility to infection.

g. Avoid aspirin and other nonsteroidal medication initially as these medications can decrease GFR.

**Statistical Analysis:** The rate of normalization of creatinine clearance, side effects, morbidity and mortality, progression to renal failure will be well studied with the various modes of therapy. Statistical significance of data will be calculated using the Student t-test. Patients clinical and serological data will be evaluated and computed at six months and one year after initiation of protocol.

**Randomization:** This will be accomplished by a flip of a coin.  
Phase I      Heads - Single daily dose; Tails - Split dose.  
PHASE II    Heads - Chlorambucil;              Tails - Pulse Medrol Rx

Patients clinical and serologic data will be evaluated and computed at six months and one year after initiation of protocol.

**Progress:**

No patients have met the criteria for the study to date.

# Detail Summary Sheet

Date: 1 Oct 82      Prot No: 82/02      Status: Ongoing  
Title:

Comparison of Bone and Joint Scans in Patients with New Onset  
Polyarthrititis or Polyarthralgias

Start Date:      Est Comp Date:  
Principal Investigator:      Facility:

MAJ Mark W. Nelson, MC

Dept/Sec:      Assoc Investigators  
Key Words:  
Bone scan; Joint scan; Arthritis

Accumulative MEDCASE	Est	Periodic
Cost	ONA Cost:	Review Results
Study Objective:		

The detection of inflammation in asymptomatic or arthralgic joints is useful for objective documentation of organic disease in medical-legal or Workman's Compensation cases and to determine early in the course of a patient the exact distribution of involved joints, therefore aiding in diagnosis (Rheumatic joint disease is classified on the basis of joint distribution). A sensitive although nonspecific test to detect such subclinical involvement would be useful. We will compare Tc99m MDP scanning reflecting metabolic activity of bone with Tc99mO<sub>4</sub> which reflects blood pool activity and is cheaper and simpler to obtain.

## Technical Approach:

Patient population: New onset polyarthrititis or polyarthralgia in adults (symptoms less than six months).

## Procedures:

I.a. A rheumatologist will make a clinical joint chart on patients noting joints where objective arthritis is present. This will be done prior to scanning.

b. The patient will then receive both scans, which will be done in the Nuclear Medicine Service under the supervision of Nuclear Medicine staff physicians. The scan will be interpreted without knowledge of the clinical joint chart and independently of each other.

II. a. The number of clinically involved joints will be compared to involved joints on bone and joint scans. A positive bone scan will be considered to be a true-positive of increased metabolic bone activity and a positive joint scan will be considered a true-positive reflecting increased flow to a joint. This applies only to activity in joint area.

b. The previously identified joints on scan will be followed to determine the long-term significance of a positive scan.

PROGRESS: Fourteen patients have been entered. No unusual occurrences have been noted. Patient accrual will continue in FY83.

# Detail Summary Sheet

Date: 1 Oct 82 Prot No: 82/03 Status: Terminated  
Title:

Emergency Treatment of Blood Dyscrasias and Lymphoid Malignancies  
with Upjohn ATGAM

Start Date: Est Comp Date:  
Principal Investigator: Facility:

MAJ J. Giri, MC

Dept/Sec: Assoc Investigators  
Key Words:  
ATGAM

Accumulative MEDCASE Cost	Est OMA Cost:	Periodic Review Results
Study Objective:		

This protocol is designed to allow the emergency treatment with ATGAM of individuals with blood dyscrasias or lymphoid malignancies in which for any reason a bone marrow transplant is either nonindicated or cannot be performed, and where in the best clinical judgment of the investigator there is no appropriate conventional therapy, or the patient is refractory to conventional therapy. Observations will be made on the effect of ATGAM on cellular elements of the circulation, general toxicity associated with administration of the drug, and the clinical outcome of the treatment.

## Technical Approach:

ATGAM will be administered in 250-1000 ml of 0.90% or 0.45% saline intravenously using an in-line filter over at least a 4-hour period (a six-hour administration period is preferred).

The optimum dose and duration of treatment in these indications has not yet been determined. ATGAM may be administered at a dose of 7-20 mg/kg body weight either daily or every other day. In the case of extended treatment periods, administration can be tapered to less frequent intervals.

Patients with blood dyscrasias such as aplastic anemia have commonly received a total of 5-21 doses. Patients with lymphoid malignancies have received up to 40 doses.

The exact dose and duration of treatment can, however, be modified to accomodate the hematological and immunological status of the individual patient. Under certain circumstances, repeat courses of ATGAM may be indicated.

**Special Considerations:**

1. All immunosuppressants including ATGAM increase susceptibility to infection. However, infection is not necessarily a contraindication to the use of ATGAM in this special setting.
2. Patient should be tested with 0.1 ml of 1:1000 dilution of ATGAM in normal saline intradermally on forearm and watched for local and/or systemic allergic reaction. 0.1 ml of normal saline given intradermally serves as control. The ATGAM skin test dose should be freshly prepared prior to each skin test.

Patients should be observed for the following reactions:

- Urticaria
- Generalized itching
- Tachycardia
- Dyspnea
- Hypotension
- Anaphylaxis (shock)

Local symptoms: Induration (wheal) and/or erythema more than 10mm with pseudopod formation and itching.

Marked local swelling of the extremity.

A systemic reaction to the ATGAM skin test precludes any further administration of ATGAM.

The predictive value of local skin test reactions has not been clinically established. Patients with locally positive skin tests have received ATGAM therapy with no untoward effects. Conversely, allergic reactions to ATGAM have occurred despite completely negative skin tests. A positive local reaction to the ATGAM skin test is not a protocol exclusion.

**PROGRESS:**

This protocol was disapproved by the HSRRB.

Detail Summary Sheet

Date: 1 Oct 82 Prot No: 82/04 Status: Ongoing  
Title:

Karyology of In Vitro Cultured Human Basal Cell Epithelioma Tissue

Start Date: Est Comp Date:  
Principal Investigator: Facility:

LTC J.E. Pryor, MC

Dept/Sec: Assoc Investigators  
Key Words:  
Basal cell epithelioma; Karyotype

Accumulative MEDCASE Est Periodic  
Cost OMA Cost:2555(2555)Review Results  
Study Objective:

To investigate chromosomal abnormalities in basal cell epithelioma cells and to initiate a cell culture line for this and further studies.

Technical Approach:

The initial efforts will be directed to previously untreated primary skin lesions of BCE. Prospective patients to be included in the study will be presented to the principal investigator for evaluation. Patients with suitable lesions requiring surgical intervention (e.g. curettage and electrodesiccation or excision) will have tissue specimens obtained, cultured, subcultured, and chromosome preparation as described by D.G. Harnden. Data concerning the tumor size, anatomic location, and approximate duration will be documented. While the specimen for tissue culture is being obtained a portion will be submitted in formalin for histologic confirmation of BCE. Once chromosome preparation is completed, coordination for karyotype determination will be made with the Dept Clinical Investigation.

Progress:

The tissue culture laboratory was equipped and supplied. Tissue from three patients has been cultured.

Due to an extremely large amount of collagenous material in the specimens obtained for culture we have been unable to adapt primary cultures for continuous cell lines. We are now employing collagenase to obtain single cell suspensions. In addition, since BCE are not known to be continuously adaptable to cell cultures, we are devising means, such as fewer layers of human foreskin, with the hope of establishing continuous cultures of BEC for further study.

### Detail Summary Sheet

Date:	1 Oct 82	Prot No:	82/05	Status:	Completed
Title: Renal Scanning as an Adjunct in Differential Diagnosis of Renal Failure					
Start Date:			Est Comp Date:		
Principal Investigator:			Facility:		
CPT Graham, MC					
Dept/Sec:		Nucl Med	Assoc Investigators		
Key Words:					
Renal scanning					

Accumulative MEDCASE	Est	Periodic
Cost	OMA Cost:	Review Results
Study Objective:		

Would a gallium scan be a useful adjunct in the diagnosis of renal parenchymal diseases

#### Technical Approach:

A total of 40 patients would be studied over two years (about 2/month).

a. All patients scheduled by nephrology staff for renal biopsy independent of study would be contacted and if both attending physician and patient concur, the patient would be entered into the study.

b. Within one month prior to biopsy the patient would be routinely scheduled for the scans.

c. The patient will be injected with 5 mCi Gallium and a spot scan of the abdomen would be done on the gamma camera and images placed on computer data bank.

d. A kidney biopsy would be completed and processed in the regular manner.

e. The scan will be read as positive or negative and graded 0 to 5+ with 0 no uptake, +4 uptake equal to liver and 5 uptake greater than liver. Computer processing would place areas of interest over center (cortical), middle and inner (medullary) areas at the midline and lower pole of the left kidney and count density obtained. Biopsy diagnosis would be obtained and degrees of inflammation in the biopsy specimen would be done by Dr Lundy without knowledge of the scan.



f. Results of biopsy and gross correlation of Ga uptake on scan would be examined for predictive accuracy in diagnosis of renal pathology. In addition Gallium uptake in different areas of scans would be compared to degree of inflammation on biopsy specimens.

Progress:

Ga-67 scintigraphy has been previously reported to be useful in the diagnosis of noninfectious interstitial nephritis. We studied twelve patients with gallium-67 citrate that were diagnosed as having noninfectious interstitial nephritis on renal biopsy. Only seven of the twelve patients with interstitial nephritis on biopsy were scan-positive. Ga-67 scintigraphy may not reliably identify noninfectious interstitial nephritis.

Detail Summary Sheet

Date: 1 Oct 81      Proj No: 82/06      Status: Ongoing  
Title:

Effect of Simultaneous Streptokinase Reperfusion with GlK,  
Nifedipine, or Hyaluronidase on Infarct Size in the Canine Heart

Start Date:      Est Comp Date:  
Principal Investigator:      Facility:

CPT R.D. Latham, MC

Dept/Sec: Dept Medicine      Assoc Investigators  
Key Words:

Myocardial infarction; Streptokinase; Nifedipine; Hyaluronidase

Accumulative MEDCA      Cost      Periodic  
Cost      MA Cost:      Review Results  
Study Objective:

Determine if the simultaneous administration of GlK or hyaluronidase, or nifedipine with streptokinase results in a significant reduction in infarct size and increased preservation of left ventricular function as compared with reperfusion alone. This protocol will also assess whether the administration of hyaluronidase or nifedipine prior to reperfusion will salvage ischemic myocardium.

Technical Approach:

Twenty large mongrel dogs will be divided into four groups of five dogs each.

- I      Streptokinase alone
- II     Streptokinase plus GlK
- III    Streptokinase plus nifedipine
- IV     Streptokinase plus hyaluronidase

Technical Approach:

Five mongrels will be anesthetized with morphine and thiopental. A mechanical ventilator will be utilized and ABG'S monitored to ensure adequate oxygenation. Surface lead II EKG and chest lead will be monitored simultaneously. Dogs will not be heparinized.

- a. A pigtail judkins catheter is placed into the left ventricle.
- b. An IV of RL will be maintained at TKO rate.

c. Control EKG on LV pressure curve will be taken. A modified judkins catheter will be utilized to cannulate the proximal LAD artery with placement of a guide wire 0/038. The wire is advanced to the apex, the catheter is removed. A copper coil, prepared in sulfuric acid and rinsed, is advanced several centimeters into the LAD using a straight cut modified judkins catheter.

d. The ECG will be monitored for development of ischemic injury, which will be allowed to remain about two hours.

e. An angiogram will be performed to assess presence of occlusion.

f. A 2F catheter will be advanced to within 1-2 mm of the thrombus.

g. A ventriculogram will be obtained.

h. Perfusion of streptokinase at a rate of 0.3 ml/min or (0.4 ml/min)(5000u/H) will be initiated.

i. Reperfusion is heralded by arrythmias. VT will be treated by 2-6 mg lidocaine IV bolus via the perfusion catheter. LV pressure will be continuously monitored.

j. An angiogram will be done to assess patency.

k. Infusion will be continued for 60 min.

l. The animal will be heparinized with a dose of 2.0 mg/kg IVP.

m. A ventriculogram will be done to assess EF and wall motion.

n. With catheters removed the animal will remain sedated with SQMS and receive heparin 10,000 units q8 h via heparin lock.

o. After 24 hours the animal will have a repeat angiogram. Monastral blue dye may be injected at this time (optional) 0.5 mg/kg over 30 seconds via a catheter in the left atrium.

p. The animal will be sacrificed using concentrated KCl solution.

q. The heart will be removed and immediately placed in ice cold water to remove excess blood. The myocardium will be cut into no greater than 1 cm slabs. Each section is weighed. A clear glass plate is placed over both sides of each slide and inner and outer margins are traced onto clear acetate with magnifying lens. Areas not perfused by monastral blue dye will also be traced. Then the

slices will be incubated in TTC to delineate the infarction. TTC will be made by combination of Trigma HCl (42.56gm) Trisma base (16.76 gm) and 2,3,5 triphenyl tetrazolium (20 gm) chloride in 2 liters of distilled water. This will be mixed and stored in the dark. Prior to incubation this solution will be warmed on a hot plate to approximately 37C. The myocardial slices will be incubated in a pan of the solution (in the dark) for about 20-30 minutes. At least 1 cm of solution covering the slices is needed. A photographic record will be obtained after placing incubated slices in normal saline solution (made by adding 17.8 gm NaCl to 2.5l of ten percent formalin).

r. Incubation in JTC at 37C will be done.

s. Estimation of infarct size will be measured from the stained myocardium, using a planimeter and plastic transparencies. Differences in weight of infarct/normal myocardium may be compared. The area at risk  $A_r$  = ratio of areas not perfused by monastral blue dye to total area of all slices. Area of necrosis  $A_n$  = ratio of areas unstained by TTC to total areas of all slices.

#### GROUP II

Will repeat above procedure with addition of GlK as solvent for streptokinase. GlK will be made by adding 50 units of insulin and 50 mEqKCl/liter D<sub>5</sub>W. Nine cc's of this solution plus 1 cc streptokinase 150,000 units/cc to be infused at 0.3 cc/min. (5400 units/hr, which is the same for all groups).

#### GROUP III

Will undergo same trial as Group I with the addition of nifedipine to the streptokinase solution (to infuse 1 mg/mKg/hr).

#### GROUP IV

Same trial as above with the addition of bovine hyaluronidase (to deliver 100 units/kg/hr).

#### Progress:

Ten dogs have been used in perfecting the technique. Early failures resulted from intractable arrhythmias.

Detail Summary Sheet

Date: 1 Oct 82      Prot No: 82/10      Status: Ongoing  
Title:

Evaluation of Saline Purge Versus Conventional Barium Enema  
Preparation in Cleansing the Colon for Air Contrast Barium Enema

Start Date:      Est Comp Date:  
Principal Investigator:      Facility:

CPT Donald R. Johnson, MC

Dept/Sec: Dept Medicine      Assoc Investigators  
Key Words:

Barium Enema

Accumulative MEDCASE      Est      Periodic  
Cost      OMA Cost:      Review Results  
Study Objective:

The purpose of this study is to compare the use of saline lavage, which we find to be an effective colonoscopy preparation, to the standard radiological preparation for air contrast barium enema used at William Beaumont Army Medical Center.

Technical Approach:

At the time the barium enema is ordered on any patient in the Gastroenterology Clinic, patient will be asked to participate in this study. Informed consent will be obtained after the study procedure is explained and the patient instruction sheet is discussed. The patient will be randomized into either the saline lavage or standard preparatory method by the GI technicians for x-ray.

Evaluation

1. Radiological
  - a. Gas, feces or fluid on the scout film.
  - b. Interference of feces, fluid or gas on contrast radiographs.
  - c. Clarity of mucosal pattern.
2. Pacing evaluation of procedure

PROGRESS: Patient entry is nearing completion. Final tabulations and analysis of data is anticipated in FY83.

### Detail Summary Sheet

**Date:** 1 Oct 82      **Prot No:** 82/11      **Status:** Ongoing

**Title:**

Serum Gentamicin Levels: Use in a Training Hospital Before and After Institution of an Intensive Educational Program.

**Start Date:**

**Est Comp Date:**

**Principal Investigator:**

**Facility:**

**MAJ Baker**

**Dept/Sec:**

**Assoc Investigators**

**Key Words:**

Serum gentamicin; Education

**Accumulative MEDCASE**

**Est**

**Periodic**

**Cost**

**OMA Cost:**

**Review Results**

**Study Objective:**

The objectives of this clinical study would be three-fold: (1) To determine when gentamicin levels are ordered by physicians caring for patients receiving this drug and to determine how frequently this information is utilized to adjust dosage and interval. (2) To determine if there is any influence on overall morbidity and mortality in the group of patients in which this information was utilized appropriately compared to the group in which it was not. (3) Having obtained this baseline data, determine any increment of change observed after the institution of an aggressive education program on the use of gentamicin levels.

**Technical Approach:**

The initial part of the study will be a retrospective review covering a 12 month period. The study population will consist of those patients on medicine wards who received at least three doses of gentamicin and had not received an aminoglycoside antibiotic within two weeks prior to entry into the study. Excluded from the study will be those patients receiving gentamicin from other services, those on hemo- or peritoneal dialysis, and those from whom complete records of hospitalization are unavailable for review.

Patients fitting the above criteria will be identified by a review of pharmacy records. From this review names, SSNs and month of hospitalization will be tabulated and submitted to inpatient records for retrieval. A standardized list of data derived from the records will be completed for each patient included in the study. A review of the radioimmunoassay laboratory records will then be performed and times and results of gentamicin levels will be recorded for each study patient.

From this data, an assessment of percentages of appropriately drawn and utilized serum gentamicin levels will be determined. A comparison of overall morbidity and mortality will be made between the group in which the procedure was used appropriately and the group in which it was not.

The second part of the study will be prospective and 12 months in duration. A list of patients receiving gentamicin will be maintained by the pharmacy. This list will be reviewed daily and those patients meeting the criteria will be entered into the study..

Having obtained baseline data and identified problem areas from the retrospective review, an educational program will be instituted just prior to initiation of the 12 month prospective study. This will consist of lectures on gentamicin pharmacokinetics, toxicity and the appropriate use of gentamicin levels. The results of the retrospective review and problem areas will be included. At two to three month intervals an update of the ongoing prospective study will be reviewed with continuing problem areas emphasized. This will be presented in depth to house staff and staff during one hour lectures, and informally to ward personnel in 30 minute in-services. One to one teaching will occur in those instances where physicians are not using or have inappropriately used gentamicin levels.

At the end of the 12 month study period the data from the retrospective and prospective study will be compared for statistically significant differences.

## 7. METHODS, DEFINITIONS:

### I Patients:

- a. The criteria for inclusion/exclusion has been outlined.
- b. Patients will be classified into three categories based on the severity of underlying disease by the criteria of McCabe<sup>16</sup>.
- c. Rapidly fatal disease: to be utilized solely for patients with acute leukemia or blastic relapse of chronic leukemia.
- d. Ultimately fatal disease: Arbitrarily based on the severity of the underlying disease rather than the specific diagnosis. The disease is likely to prove fatal within the next five years. Patients with carcinoma, with proved metastases, myeloma, lymphoma, aplastic anemia, severe renal failure and liver disease with spontaneous coma or bleeding esophageal varicies to be included in this group.
- e. Non-fatal: The underlying disease is considered unlikely to be fatal within the next five years.

## II. Morbidity

### a. Nephrotoxicity

A rise in serum creatinine of 0.5 mgm% or greater if initial level is less than 3 mgm%, or a rise in serum creatinine of 1 mgm% if initial creatinine is more than 3 mgm%.

b. Ototoxicity - gross abnormalities, i.e. deafness, ataxia or nystagmus occurring during therapy. Audiometry and aloric testing will not be performed.

c. Length of hospital stay.

## III Mortality:

All deaths which occur within 7 days of onset of bacteremia will be considered due to bacteremia unless a 2nd usually lethal event, not associated with or precipitated by bacteremia occurred and there is strong clinical evidence of recovery from the episode of bacteremia. Adapted from McCabes definition<sup>16</sup>.

## IV Use of gentamicin levels:

### a. Defined as:

Therapeutic - peak serum concentration of 4-12 ug/ml

Sub-therapeutic - peak serum concentrations of less than 4 ug/ml

Toxic - Peak serum concentration of more than 12 ug/ml or trough serum concentrations more than 2 ug/ml

### b. Time of sampling (correctly drawn)

Peak - drawn 30 minutes after an IV infusion

Trough - drawn just prior (within 30 minutes) of IV infusion

### c. Use of levels obtained as correctly drawn peaks/trough pairs will be classified as appropriate if:

(1) The peak and trough is in the therapeutic range and the dose is not changed.

(2) Peak is more than 12 ug/ml and the dose is decreased.

(3) Peak is less than 4 ug/ml and the dose is increased.

(4) Trough is more than 2 ug/ml and the interval is increased.

(5) Any combination of the last three.



## V. Data analysis.

a. At the conclusion of the retrospective study, the percentage of patients having appropriately drawn and utilized levels will be tabulated. Comparisons will be made of these patient categories, defined by severity of underlying disease, who had serum gentamicin levels drawn and utilized appropriately and those who did not. The influence of inappropriately drawn gentamicin levels on overall morbidity and mortality as defined will then be assessed.

b. At the conclusion of the prospective study the percentage of patients who had appropriately drawn and utilized levels will be compared to the retrospective group. If there is a significant difference between the prospective and retrospective group, the influence on overall morbidity and mortality will be assessed. The influence of the education program can then be measured.

### Progress:

One thousand names have been obtained from the Pharmacy. These patients were all treated with gentamicin. Record retrieval and collection of data will progress throughout FY83.

### Detail Summary Sheet

Date: 1 Oct 82      Prot No: 82/12      Status: Terminated

**Title:**

Utility of oral calcium administration in the prevention of acute renal failure (ARF) in patients treated with aminoglycoside.

Start Date:

Est Comp Date:

Principal Investigator:

Facility:

MAJ M. Siedlecki, MC

Dept/Sec: Renal

Assoc Investigators

Key Words:

Oral calcium; Aminoglycoside

Accumulative MEDCASE  
Cost

Est  
OMA Cost:

Periodic  
Review Results

Study Objective:

To test the efficacy of oral calcium administration in the prevention of aminoglycoside caused ARF.

**Technical Approach:**

A. Patient Selection. All patients requiring aminoglycoside treatment will qualify for the study except:

(1) Those diabetic patients with glucosuria. This is because it has been shown that solute diuresis protects against G toxicity.

(2) Patients with hypercalcemia above 10.5 mEq/dl.

(3) Patients treated with Verapamil nithilmycin, Nefetipin, MgSO<sub>4</sub>, Methacillin, cephalosporins, amphotericin.

(4) Patients with malabsorption and known vitamin D deficiency.

(5) Patients with known chronic renal disease.

Clinical volume depletion, shock, and other clinically known nephrotoxins such as radiocontrast dye agents, will be avoided if possible.

B. Plan of proposed investigation. There will be two patient groups, A and B, and 10% molasses (placebo) will be provided by the Pharmacy to satisfy a randomized double blind method of study. It is proposed to study a minimum of 40 patients. A standard dose of 1.5 mg/kg/8 hrs of gentamicin will be used.

Group A, Calcium Group: 3 gm of elementary calcium in the form of liquid Neo-Cal-Glucon<sup>K</sup> (1 cc = 19 mEq Ca++) will be administered orally in three divided doses, 1 gm or 49 ml with three main meals of the day. This will be given for the duration of aminoglycoside therapy.

Group B, Placebo Group. Equal amounts of molasses tonic (10% molasses in water) will be administered in a similar fashion to the A Group.

C. Laboratory determinations. In addition to standard laboratory use dictated by currently accepted medical care, daily monitoring of serum Ca++ and possibly PO<sub>4</sub> will be required. This is necessary to ensure and monitor serum Ca++ due to oral administration. Also patients will be monitored with urinalysis (done by a physician) and serum creatinine, and possibly urea, on an every other day basis for an additional 5 days after completion of the scheduled aminoglycoside treatment. All laboratory determinations will be recorded from the SMAC-20 since there is a wide discrepancy between STAT and SMAC-20 values in our hospital. Gentamicin levels will be collected on day 2 of treatment for peak and trough levels and if more than 12 or 2 ug/ml respectively, dose will be adjusted. Note that most commonly, aminoglycoside toxicity is noted after the fifth day of treatment and within 5 days after completion of the usual 10 day antibiotic course. Patients treated less than five days will not be considered in the statistical analysis. Lastly, B<sub>2</sub>-microglobulin will be measured every other day in both patient groups.

D. Data Evaluation: Nephrotoxicity will be defined as a rise in serum creatinine of 0.5 mg%(44.2 uMol/L) or more if the initial level was more than 3.0 mg%(265.2 uMole/L) or a rise of 1.0 mg% or more if the initial creatinine was 3.0 mg% or less [8]. Note that the definition of nephrotoxicity is purely arbitrary and varies from author to author. In the present study it is just necessary since we have double blind prospective controls.

#### Progress:

The principal investigator was reassigned shortly after activation of this protocol. No progress was reported.

# Detail Summary Sheet

Date: 1 Oct 82      Prot No: 82/13      Status: Ongoing  
Title:

Infection Induced Kidney Stones: A Multi-Center Clinical Trial of UROSTAT<sup>TM</sup> (Acetohydroamic Acid)

Start Date:      Est Comp Date:  
Principal Investigator:      Facility:

MAJ A.R. Henry, MC

Dept/Sec: Dept Medicine      Assoc Investigators  
Key Words:      MAJ S.F. Gouge    MAJ JC Norbeck  
UROSTAT      MAJ JE Crosse MC

Accumulative MEDCASE      Est      Periodic  
Cost      OMA Cost:      Review Results  
Study Objective:

To ascertain the effectiveness of aceothydroxamic acid (AHA) in the prevention and/or dissolution of infection - induced urinary stones and to study the safety of AHA with respect to side effects.

## Technical Approach:

A two year, double-blind study will be conducted in patients with chronic urea-splitting urinary infection that is recalcitrant to effective antimicrobial treatment. The code may be broken and the patient may be placed on the best treatment available, including AHA if there is unequivocal stone growth. Patients will be permitted an ad lib diet, and they may take their usual medications, including antibiotics. Clinical, laboratory, radiographic and compliance data will be recorded.

Patients with recalcitrant urea-splitting urinary infection and/or infected renal calculi are candidates. Patients may have infection-induced stones or they may be surgically stone-free. Patients are ineligible if:

Their urine is infected by an organism that does not make urease (i.e., split urea).

Their urine can be chronically sterilized with culture-specific oral antimicrobial agents.

Their renal function is poor (i.e., serum creatinine greater than 3.0 mg/dl).

They become pregnant.

Satisfactory effort of contraception is not evidenced by female candidates.

Life-threatening disease involving other organ systems is co-existent.

In the opinion of the attending physicians the risks induced by treatment are likely to outweigh the potential benefits.

Patients may be dropped from participation because of:

Non-compliance (i.e., failure to take medication reliably, failure to return for followup visits and tests, failure to report side effects).

Adverse effects.

Patients may terminate their participation by discontinuing their medication at any time. Such withdrawal will not cause ill will by those providing their care.

Progress:

This is a new IND study. Patient entry was approved near the end of FY82.

Detail Summary Sheet

Date: 1 Oct 82 Prot No: 82/15 Status: Completed

Title:

Usage of Cromolyn in Topical Treatment of Allergic Skin Reactions

Start Date:

Est Comp Date:

Principal Investigator:

Facility:

MAJ S. Ting, MC

Dept/Sec: Dept Medicine

Assoc Investigators

Key Words:

Topical cromolyn

Accumulative MEDCASE

Est

Periodic

Cost

OMA Cost:\$121(121) Review Results

Study Objective:

To determine whether locally applied cromolyn suppresses the histamine release, eosinophil migration response, and ultrastructural changes of mast cells in human allergic skin reactions.

Technical Approach:

Twenty volunteers from the Allergy Clinic will be skin tested with ragweed, Russian Thistle and Cromolyn 2% or 4% and the size of the wheals recorded. They will then be intradermally injected with 0.02 ml of 2% or 4% cromolyn and after 30 minutes testing repeated. Using a skin blister technique the following will be accomplished

- a. Charge Chamber A with ragweed 1000 PNU/CC
- b. Charge Chamber B with PBS (phosphate buffered saline
- c. Charge Chamber C with ragweed 1000 PNU/cc and cromolyn 2%
- d. Charge Chamber D with cromolyn 2%

Samples will be placed in prelabeled vials on ice and frozen. Collecting chambers will be removed. Filters will be placed on the base of each blister and secured with plastic backing and tape. In two hours this will be removed and placed in alcohol for future staining and counting of eosinophils. Filters will be stained using chromotrope 2R stain, mounted and read in numbers of eos per mm<sup>2</sup>. Filters will be saved for future recounting. The volunteer will place bandaids coated with antibiotic ointment overall denuded sites and return home.

## Progress:

Cromolyn pre-treatment frequently reduces antigen-inhalation-induced bronchospasm possibly by inhibiting mast cell degranulation and mediator release. However, the local effects of Cromolyn on Type I hypersensitivity skin reactions are not well understood.

Twelve atopic volunteers were skin tested intradermally. Mean  $\pm$  SEM mm<sup>2</sup> whealing responses were: Ragweed 1000 PNU/ml = 593  $\pm$  33, Control Phosphate buffered saline = 0, Ragweed 1000 PNU/cc + Cromolyn 2% = 619  $\pm$  27, Cromolyn 2% = 10  $\pm$  3. Pretreatment of the skin with local cromolyn 2% did not influence the allergen induced skin reactions.

Using a previously described skin blister technique we added to Chamber A: Ragweed extract 1000 PNU/cc, to Chamber B: Buffered saline control fluid, Chamber C: Ragweed 1000 PNU/ml and Cromolyn 2%, to Chamber D: Cromolyn 2% alone. Mean  $\pm$  SEM histamine levels after 30 minutes incubation were: Chamber A - 21  $\pm$  2.6 ng/ml, Chamber B - 4  $\pm$  0.85 ng/ml, Chamber C - 21  $\pm$  1.26 ng/ml, and Chamber D - 5  $\pm$  0.4 ng/ml. Local eosinophilic responses to antigen was not inhibited by Cromolyn. Thus, unlike the situation in the lungs, allergic skin reactions and associated events are not inhibited by local Cromolyn application.

Cromolyn has been shown to inhibit histamine release from mast cells induced by various stimuli in vitro. Injection of codeine in human skin results in prominent whealing, likely due to histamine release. Little is known about the in vivo effect of cromolyn on these codeine reactions. Using a previously described skin chamber technique we added to Chamber A codeine 1%, Chamber B buffered saline control fluid, Chamber C codeine 1% and cromolyn 2%, Chamber D cromolyn 2% alone. Mean  $\pm$  histamine levels after 30 minutes incubation were: Chamber A 19.4  $\pm$  7.9 ng/ml, Chamber B 3.6  $\pm$  1.0 ng/ml, Chamber C 19.6  $\pm$  7.2 ng/ml and Chamber D 4.2  $\pm$  0.86 ng/ml. Thus, unlike the situation in vitro, codeine induced histamine release in vivo is not inhibited by cromolyn.

Detail Summary Sheet

Date: 1 Oct 82 Prot No: 82/16 Status: Completed

Title:

The Usage of Calcium Antagonist (Verapamil) in Topical Treatment of Allergic Skin Reactions

Start Date:

Est Comp Date:

Principal Investigator:

Facility:

MAJ S. Ting, MC

Dept/Sec: Dept Medicine

Assoc Investigators

Key Words:

Verapamil

Accumulative MEDCASE  
Cost

Est

Periodic

OMA Cost:\$292(292) Review Results

Study Objective:

To determine whether verapamil calcium antagonist (slow channel blocking agent) inhibits allergen induced skin reactions.

Technical Approach:

Study Group A:

Twenty adult volunteers from the Allergy Clinic.

1. Skin testing will be performed with ragweed, Russian thistle, and Verapamil (nontoxic concentration established at our clinic.

2. Skin testing procedure - inject

Intradermally 0.02ml RW	1000PNU/ml,	Russian thistle	1000PNU/ml.
Intradermally 0.02ml RW	500PNU/ml,	Russian thistle	500PNU/ml.
Intradermally 0.02ml RW	1000PNU/ml,	Russian thistle	100PNU/ml.
Intradermally 0.02ml RW	10PNU/ml,	Russian thistle	10PNU/ml.

3. Wait 15 minutes.

4. Record the size of the wheal and flare reactions.

5. Intradermally inject 0.02 ml of 25ug/ml of Verapamil.

6. Wait 30 minutes and repeat steps 2, 3, and 4 at the skin sites previously injected with Verapamil.



7. Proceed to skin blister technique.

Introduced into Chamber A. - Ragweed 1000 PNU/cc.  
Chamber B. - PBS(Phosphate Buffered Saline)  
Chamber C. - Ragweed 1000 PNU/cc + 10mg/ml Verapamil.  
Chamber D. - Verapamil 10 mg/ml.

8. Incubate 30 minutes.

9. Remove all chamber fluid for analysis of histamine.

10. Skin Biopsy Experiments:

a. Inject intradermally 0.02ml of the final concentration of Ragweed 1000 PNU/cc + 25ug/ml Verapamil on the outer aspect of the right upper arm.

b. Inject intradermally 0.02cc of Verapamil 25ug/ml on the outer aspect of the left arm.

c. Ten minutes afterward a 3mm punch skin biopsy will be taken from both sites under local anesthesia of 1% xylocaine. The specimen will be sent to EM laboratory for analysis of mast cell changes.

STUDY GROUP B

To take verapamil 20 mg orally or sublingually.

Wait 45 minutes - repeat skin testing as Study Group A-1, A-2, A-3 and A-4.

Progress:

Calcium antagonists have been reported to inhibit allergen induced histamine release from basophils and mast cells in vitro. Furthermore, a recent study suggests the calcium antagonist nifedipine inhibits Type I skin reactions in an animal model. No comparable information exists concerning the effects of a calcium antagonist on the human IgE mediated skin test response or on the pharmacologically-induced skin test reaction. In this study we evaluated the effects of verapamil in non-irritant dosage on the human skin test response to allergen and compound 48/80.

Ten ragweed (RW) sensitive allergic volunteers were skin tested with .02 ml intradermally of the following solutions: phosphate buffered saline control (PBS); RW 500 PNU/ml; RW 500 PNU/ml plus 25 mg/ml V. There was no response to PBS. RW alone produced X wheal response of  $346 \pm 17 \text{ mm}^2$ . RW + V wheal response was  $37 \pm 16 \text{ mm}^2$ . In five other RW sensitive volunteers, the concentration of RW and 48/80 to produce 5 mm diameter wheals was established ( $\text{ED}_{50}$ ). Two sites on the forearm 8 cm apart were injected with 0.75 ug V. After a 30-minute wait, each site was challenged with either the  $\text{ED}_{50}$  dose of RW or 48/80. The response at the V-treated sites was the same as at untreated sites. Electronmicroscopy studies revealed that V treatment did not affect RW or 48/80 induced degranulation of skin mast cells. Thus, unlike the situation in vitro and in vivo animal studies, the ragweed and compound 48/80 induced skin reactions are not inhibited by verapamil.

# Detail Summary Sheet

Date: 1 Oct 82      Prot No: 82/18      Status: Ongoing

## Title:

The Use of a Combination of Isoelectric Focusing, Inhibition Radioautography and Enzyme Labelling to Determine Cross-Reacting Allergens.

Start Date:

Est Comp Date:

Principal Investigator:

Facility:

LTC L.E. Mansfield, M.D.

Dept/Sec: Dept Medicine

Assoc Investigators

Key Words:

Cross-reacting allergens

R.F. Frederick, Ph.D

Accumulative MEDCASE

Est

Periodic

Cost

OMA Cost:

Review Results

Study Objective:

To determine if a novel approach using a combination of isoelectric focusing and radioautography and enzyme labelling will be useful in determining cross-reacting allergens of pollen extracts.

## Technical Approach:

1. Technical consideration for optimum analytic isoelectric focusing of pollen extracts will be worked out for our laboratory.

2. After this stage has been accomplished, a technique for electroblotting the separated protein bands on paper will be utilized. This procedure will end any significant diffusion of the proteins and make possible Step 3.

3. The paper will be overlaid with human allergic serum specific to the pollens involved. The paper will have been previously treated so that nonspecific binding of serum globulins on the paper cannot occur. After the overlaying and antigen-antibody reaction, the paper will be washed to remove any serum protein not immunochemically bound to the allergen proteins. The next step will be a second overlay with radiolabeled anti-human IgE (FC Specific). This will be followed by another gentle washing. The paper will be dried and placed on an x-ray film for radioactive exposure of the film. Lines of interest should develop where human IgE antibodies have bound to the allergen proteins.

4. In the enzyme labeling technique anti-human IgE chemically bound to horse radish peroxidase will be used as the

marker rather than the radiolabel. The bands will be subjected to a colorimetric reaction catalyzed by enzyme conjugate. The intensity of the reaction will be read by spectrophotometric methods.

5. In this step the human allergic sera will be preincubated with an allergen extract suspected of containing cross-reacting proteins to the allergen extract, electrophoresed and transferred to paper. The incubated sera will be used in the same manner as described in Steps 3 and 4.. Absence or diminution of intensity of the bands on the x-ray film will occur if the allergen extract contains proteins which cross react with allergens in the first extract.

#### Progress:

Each of the three techniques is now available in the Department of Clinical Investigation. Study of the antigens is underway, but preliminary, as this is a relatively newly approved protocol.

# Detail Summary Sheet

Date: 1 Oct 82      Prot No: 82/20      Status: Ongoing

## Title:

An Investigation Into Possible Bronchoconstrictive Reflexes Arising with Gastric Distention in Asthmatic Subjects

Start Date:

Est Comp Date:

Principal Investigator:

Facility:

LTC L.E. Mansfield, MC

Dept/Sec: Dept Medicine

Assoc Investigators

Key Words:

Asthma; Gastric distention

Accumulative MEDCASE

Est

Periodic

Cost

OMA Cost:

Review Results

Study Objective:

To discover if gastric distention causes a bronchoconstrictive response in asthmatic subjects. To determine if pretreatment with atropine ablates this response.

## Technical Approach:

Twenty adult asthmatic patients will be selected at random from the allergy immunology clinic population. They will come to the clinic at 0800 (having omitted their morning bronchodilators if tolerated). Total respiratory resistance will be measured by the method of forced oscillations and then conventional spirometric and flow-volume determinations will be performed.

Each subject will drink 20 oz. of water. All pulmonary functions in the same order as at baseline will be repeated. The subject will continue drinking water until he/she experiences the sensation of fullness (as after eating a bit too much). Pulmonary function tests will be repeated.

If the airway response to gastric distention, as measured by pulmonary functions, is compatible with bronchoconstriction, then the five patients in whom this response was most dramatic will be reinvestigated to determine if atropine will inhibit this reaction. These patients will report on a second day at 0800 omitting bronchodilators, if possible. Baseline pulmonary functions will be determined, two mg. atropine sulphate will be delivered to the patient by aerosol nebulization. A post-atropine baseline will be established 15 minutes after this treatment. The same procedure as outlined above will be followed concerning water ingestion and pulmonary function determinations.

The results will be analyzed by appropriate parametric and nonparametric statistics.

**Progress:**

Patient entry had just begun on this new protocol at the close of FY82.

Detail Summary Sheet

Date: 1 Oct 82      Prot No: 82/21      Status: Ongoing  
Title:  
The Incidence of Gastroesophageal Reflux and Microaspiration Among Adult Asthmatics.

Start Date:      Est Comp Date:  
Principal Investigator:      Facility:  
CPT Gordon D. Graham, M.D.

Dept/Sec: Dept Medicine      Assoc Investigators  
Key Words:  
Asthma; Gastroesophageal reflux

Accumulative MEDCASE      Est      Periodic  
Cost      OMA Cost:      Review Results  
Study Objective:

To determine, using a new improved capsule technique, the incidence of microaspiration in adult asthmatics.  
To determine how frequent gastroesophageal reflux is in a mixed series of adult asthmatics.

Technical Approach:

Two hundred consecutive adult asthmatic patients who require daily bronchodilators will enter the study. The nature and purpose of the study will be explained to them. They will be sent to Nuclear Medicine Service to have a scan for the presence or absence of reflux, as described below. If reflux is demonstrated, they will have a second scan to investigate the possibility of microaspiration, again as described below.

Upon referral from the Allergy Clinic, the patient would be scheduled for a routine gastroesophageal reflux study. A dose of TcSCOL in a gelatin capsule is administered orally and the patient is then given six cups of water to drink. Subsequently a scan is performed in the anterior view while the patient is in a trendelenburg position.

If reflux is demonstrated, a second study would be scheduled in two weeks. The patient would be scheduled for a capsule of Tc SCOL orally at 8 pm after a heavy evening meal. The subsequent morning an anterior and posterior scan would be done of both lung fields.

Progress:

Patient entry has not begun on this new protocol.

Detail Summary Sheet

Date: 1 Oct 82	Prot No: 82/22	Status: Ongoing
Title: Use of Topical Steroid Cordan Tape (Fluorandrenolide) in the Management of Skin Reactions		
Start Date:	Est Comp Date:	
Principal Investigator: MAJ S. Ting, MC	Facility:	
Dept/Sec: Dept Medicine	Assoc Investigators	
Key Words: Fluorandrenolide; Skin reactions		

Accumulative MEDCASE Cost	Est OMA Cost:	Periodic Review Results
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Study Objective:

To determine whether locally applied cordan tape suppresses the histamine release, eosinophil migration and ultrastructural changes of mast cells in human allergic skin reaction.

Technical Approach:

Ten volunteers from the Allergy Clinic will be skin tested with ragweed and 48/80. Injections will be 0.02 ml of ragweed 1000 PNU/cc and 48/80. Skin blister technique will be employed and cordan tape placed over both forearms for 24 hours, then skin biopsy to determine measurement of histamine release.

Progress:

Patient entry is nearly complete. The data will be analyzed and reported in FY83.

# Detail Summary Sheet

Date: 1 Oct 82 Prot No: 82/23 Status: Ongoing

## Title:

Use of Hydroxyzine HCL (Atarax) in the Treatment of Allergic Skin Reactions

Start Date:

Est Comp Date:

Principal Investigator:

Facility:

MAJ S. Ting, MC

Dept/Sec: Dept Medicine

Assoc Investigators

Key Words:

Atarax; Skin reactions

Accumulative MEDCASE

Est

Periodic

Cost

OMA Cost:

Review Results

Study Objective:

To determine whether orally administered antihistamine (Atarax) blocks the allergen-induced histamine release and ultrastructural changes of mast cells.

## Technical Approach:

Ten volunteers from the Allergy Clinic will be skin tested with ragweed and 48/80.

a. Skin testing injections 0.02 ml of ragweed 1000 PNU/cc and 48/80 1000 PNU/cc.

b. Wait 15 minutes.

c. Record the size of the wheals and flares.

d. Proceed to skin blister technique for the measurement of histamine release.

e. Using a skin blister technique -

(1) Charge Chamber A with ragweed 1000 PNU/cc

(2) Charge Chamber B with PBS (phosphate buffered saline).

(3) Charge Chamber C with 48/80.

(4) Charge Chamber D with Ragweed 500 PNU/cc.

f. Place samples in pre-labeled vials on ice and freeze.

g. Remove collecting chambers.

h. Place Metricell (.45uM) filters on the base of each blister, secure with plastic backing and tape.

i. Remove in 2 hours, place in alcohol for future staining and counting of eosinophls.



- j. Stain filters using chromotrope 2R stain.
- k. Mount and read numbers of eos per mm<sup>2</sup>
- l. Save all mounted filters for future recounts.
- m. Volunteer places bandaids coated with antibiotic ointment over all denuded sites and returns home.
- n. Atarax 25 mg q.i.d. x 3 days and repeat.
- o. Proceed to skin biopsy technique.

Progress:

Patient entry is nearly complete. The data will be analyzed and reported in FY83.

### Detail Summary Sheet

Date: 1 Oct 82	Prot No: 82/24	Status: Ongoing
Title: An Investigation into the Anticholinergic and Local Anesthetic Properties of Cromolyn		
Start Date:	Est Comp Date:	
Principal Investigator: LTC L.E. Mansfield, MC	Facility:	
Dept/Sec: Dept Medicine	Assoc Investigators	
Key Words: Cromolyn; Anticholinergic agent		

Accumulative MEDCASE Cost	Est OMA Cost:	Periodic Review Results
Study Objective:		

To determine if cromolyn sodium has any anticholinergic or local anesthetic properties.

#### Technical Approach:

Ten normal volunteers will be chosen from the patients and the staff of this hospital. The following studies will be performed.

a. Pure cromolyn powder will be applied to a small patch of the buccal mucosa. A similar area will be treated with placebo powder. The threshold of sensation will be determined by a pain response to a calibrated electric stimulus in both treated and contiguous untreated area.

b. Three cutaneous blisters will be raised by a vacuum blister technique. The blisters will be denuded. Pure cromolyn powder will be applied to one blister site. A second blister site will have placebo powder applied. The threshold response to citric acid will be determined at the treated and untreated sites, using twofold increasing concentrations of citric acid.

c. 0.1 ml of 4% cromolyn solution will be injected subcutaneously into a skin site, 0.1 ml 1% lidocaine, and 0.1 ml placebo solution will be injected into similar sites. Each site and an untreated site will be challenged with 0.1 ml of 0.1 mg per ml methacholine subcutaneously. The size of the methacholine wheal will be measured.

d. This will be the same procedure as in Step 3 except that compound 48/80 will be used to develop the wheal.

e. The forearm sites will be treated as in Step 3, with two additional sites - one injected with 0.1 ml of propranolol 25 mg/ml and one injected with 0.1 ml of a solution combining 4% cromolyn and 25 mg/ml propranolol. The arms will be encased in a plastic bag to induce sweating. Each treated site will be covered with carefully weighed absorbent filter paper disc and a nonporous cover. After sweating has been induced, the filter paper will be removed and weighed to determine the amount of perspiration at each site.

f. These studies will be performed over a period of four weeks.

g. The results will be analyzed to determine if any anticholinergic or local anesthetic effects are seen with the cromolyn treatment.

h. Pure cromolyn powder without lactose will be provided by the Fisons Corp. 4% cromolyn solution will be provided by Fisons Corp.

Progress:

This protocol has not been activated pending the availability of resources.

# Detail Summary Sheet

Date: 1 Oct 82 Prot No: 82/34 Status: Terminated  
 Title:  
 The Efficacy of an Ophthalmic Solution of 2% Cromolyn in Treating Seasonal Allergic Conjunctivitis  
 Start Date: Est Comp Date:  
 Principal Investigator: Facility:  
 LTC L.E. Mansfield, MC  
 Dept/Sec: Dept Medicine Assoc Investigators  
 Key Words:  
 Ophthalmic cromolyn

Accumulative MEDCASE Est Periodic  
 Cost OMA Cost: Review Results  
 Study Objective:

The efficacy of the 2% cromolyn solution in treating allergic conjunctivities without the 2 P.E. preservative will be investigated.

## Technical Approach:

Twenty adult nonpregnant patients, with a history of daily eye symptoms, during the period August through October (weeks of pollen season) will be entered into the study. They will not have received allergen, immunotherapy for one year prior to the beginning of the study. They will have 3+ or 4+ prick puncture skin tests to these late summer-fall aeroallergens. The study will commence on or about 1 Aug 1982. In a random double blind fashion the patient will be placed in the following treatment groups:

Active	Placebo
Cromolyn sodium 2%	Sodium phosphate 1.91%
EDTA 0.01%	Sodium chloride 0.34%
Benzalkonium Cl 0.01%	Sodium biphosphate 0.21%
	EDTA 0.01%
	Benzalkonium Cl 0.01%

For the first week of August the subjects will use no medications (except on an as needed basis). It is not expected that symptoms will be very great at this time. Each subject will have a complete ophthalmologic evaluation performed. During the second week they will begin intraocular instillations of their eye solutions, one drop in each eye six times daily. During the entire study, including the baseline period, patients will keep daily symptom/medication scores. They will be seen in the allergy-immunology service on a weekly basis to collect and review diary cards of the previous week and to dispense prescriptions for medications. All medications for the study will be kept and recorded in the central pharmacy.

There will be no crossover of active and placebo subjects. Since it is recognized that symptoms may occur such as allergic rhinitis in the subjects, the following medications will be used on a prn basis for nasal symptoms. These will be recorded in the symptom medication diary:

Afrin nasal spray, q 8 hr, for up to 3 days.

Beclomethasone 100 ug, 4 times a day (50 ug each nostril), for up to two weeks if Afrin is insufficient to supply relief of nasal symptoms.

H-1 histamine antagonists will not be used because of their possible effects on ocular symptoms. If ocular symptoms should become intolerable to the subjects in the study, they will use collyrium eyedrops, one drop each eye every 3-4 hours prn. This use will be recorded. A need to use more potent ophthalmic agents to treat allergic conjunctivitis will disqualify the patient from further participation in the study.

The issuance of prn medications will be after examination by the study investigators, who will be on call for the study patients during the study period. During the fourth week of the study the subjects will have a repeat complete ophthalmologic examination.

For the entire six weeks of medication use, the patient will be seen as mentioned once weekly in the allergy-immunology clinic by ST or LM. The study will terminate after the six weeks of medication use. At that time treatment will be provided for continuing patient care.

At the conclusion of the study period the subjects will have a final ophthalmologic examination.

Statistical analysis of symptom/medication scores for the two groups will be performed and compared. Daily pollen counts will be performed during the time of the study by the allergy-immunology service. An IND 9114-1 has been submitted by Fisons Corp.

#### Progress:

The protocol was approved at all levels, including HSRRB. The principal investigator elected not to pursue the study. No patients were entered.

Detail Summary Sheet

Date: 1 Oct 82 Prot No: 82/35 Status: Ongoing  
Title:  
Skin Response to 48/80 and Codeine in Patients with Atopic Dermatitis  
Start Date: Est Comp Date:  
Principal Investigator: Facility:  
MAJ S. Ting, MC  
Dept/Sec: Dept Medicine Assoc Investigators  
Key Words:  
Atopic dermatitis; Histamine degranulators

Accumulative MEDCASE Est Periodic  
Cost OMA Cost: Review Results  
Study Objective:

To determine whether locally applied histamine degranulator(s) such as 48/80 and codeine induce increased histamine release in diseased skin versus normal skin.

Technical Approach:

Twenty adult patients will be selected from the allergy clinic. They will undergo skin testing, skin chamber study and skin biopsy.

- a. Skin testing will be performed with 48/80 and with codeine.
- b. Skin testing procedure: Inject intradermally 0.02 ml of 48/80 mg/ml and intradermally 0.02 ml of codeine 1% on normal skin and on skin with atopic dermatitis.
- c. Wait 15 minutes. Record the size of the wheal and flare section.
- d. Skin blister technique:

Introduce into chambers A - 48/80  
B - control saline  
C - codeine 1%  
D - control saline

- e. Incubate 30 minutes. Remove all chamber fluids for analysis of histamine.
- f. Skin biopsy:  
Inject intradermally 0.02 ml of 48/80  
10 minutes later, using a disposable 3mm punch skin biopsy set, a small amount of skin will be removed under 1% xylocaine. The specimen will be sent to the electromicroscopy laboratory for electromicroscopic analysis of mast cell changes.

Progress:

This protocol has not been activated pending revision and final committee acceptance.

# Detail Summary Sheet

Date: 1 Oct 82	Prot No: 82/41	Status: Completed
Title: The Effect of Pollen Ingestion on the Immediate Skin Test Reaction to Allergen, 48/80, Histamine and Codeine		
Start Date:	Est Comp Date:	
Principal Investigator: LTC L.E. Mansfield, MC	Facility:	
Dept/Sec: Dept Medicine	Assoc Investigators	
Key Words: Bee pollen		

Accumulative MEDCASE Cost	Est OMA Cost:	Periodic Review Results
Study Objective:		

By use of the immediate skin test reaction as model, to evaluate the possibility that the folk habit of eating "bee pollen" to treat allergic rhinitis has a nonplacebo basis.

## Technical Approach:

Fifteen to twenty adult subjects who intermittently treat themselves with the same "bee pollen" will undergo titrated prick skin tests on their backs to an allergen to which they are highly sensitive, to 48/80, to codeine, and to histamine in increasing two-fold dilutions.

After testing the patient will take capsules containing 300 mg of bee pollen. They will be retested on the seventh day. All reagents will be made fresh weekly from concentrated stock solutions of 50% glycerin for stability. All testing will be done at the same time of the day to avoid problems with circadian variations in skin reactivity.

The testing to each reagent on the two occasions will be compared by statistical analysis. A 3mm skin wheal or greater will be considered a positive test for analysis. The comparison made will be between the lowest concentrations previous to and after treatment which cause this response.

## Progress:

The use of "bee pollen" to treat symptoms of allergic rhinitis is an old custom. This practice has been revived with the recent public

interest in natural foods and natural cures. To investigate if there was a rational basis for this practice, the effects of ingesting bee pollen on allergens, codeine, 48/80, and histamine skin testing was evaluated. After baseline testing, which was performed by two-fold dilution prick skin testing on the back to various allergens and the pharmacologic agents, the subjects ingested increasing doses of commercially available "bee pollen" capsules. After a week, when they were ingesting 3 gm daily, the testing was repeated. Fifteen of 20 subjects showed a decrease in allergen skin test reactivity. ( $P = .01$ ), no statistical differences were found in 48/80, histamine or codeine testing. The "bee pollen" used consisted mainly of mesquite pollen, which was unrelated to the tested allergens. These results suggest that there may be a rationale for the folk habit of treating hay fever with bee pollen. Furthermore, the mechanism does not appear due to antihistaminic or mast cell mediator depleting activity.



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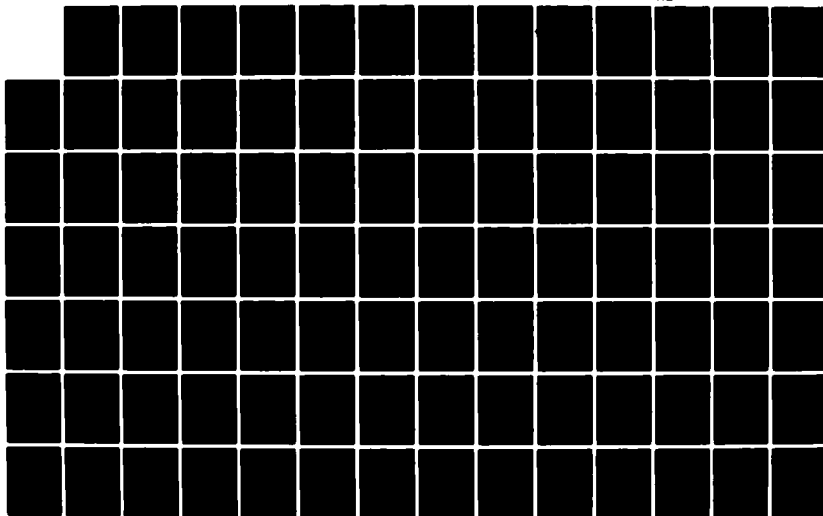
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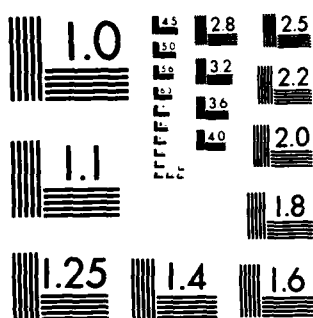
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# Detail Summary Sheet

Date: 1 Oct 82 Prot No: 82/47 Status: Ongoing  
 Title:  
 Effect of Naloxone on B-Endorphin Response to Exercise  
 Start Date: Est Comp Date:  
 Principal Investigator: Facility:  
 LTC D.M. Suich, MC  
 Dept/Sec: Dept Medicine Assoc Investigators  
 Key Words:

B-endorphin; Naloxone; Exercise

Accumulative MEDCASE	Est	Periodic
Cost	OMA Cost:\$400(400)	Review Results
Study Objective:		

It has been established that intense exercise induces an increase in plasma B-endorphin levels in human beings. The objectives of this study are two-fold: (a) to confirm that the levels of exercise obtained in a previous study were indeed sufficient to induce elevation of plasma B-endorphin levels; and (b) to establish if the elevation of plasma B-endorphin induced by exercise is enhanced in the presence of a specific opiate antagonist, Naloxone.

## Technical Approach:

The plasma specimens to be evaluated were obtained while conducting a previous protocol. There are two sets of specimens. The first group consists of six paired specimens representing plasma obtained before exercising six subjects and at the completion of exercise of the six subjects. The exercise protocol consisted of a progressive, graded, multistaged bicycle exercise test lasting approximately 30 minutes. The second group consists of five paired sets of 3 to 4 specimens obtained from repeat exercise studies in five of the six subjects. These specimens were obtained pre-exercise, 25 minutes into exercise and at the end of exercise. In all the preceding samples one of the pair was collected when the subject received naloxone and the other with placebo, saline.

## Progress:

A portion of the samples have been analyzed for B-endorphin by radioimmunoassay. The remainder should be completed, and the original specimens verified, in FY83.

# Detail Summary Sheet

Date: 1 Oct 82	Prot No: 82/50	Status: Ongoing
Title: Effect of Long Term Treatment with Cromolyn Sodium on Nonspecific Bronchial Hyperreactivity		
Start Date:	Est Comp Date:	
Principal Investigator: LTC L.E. Mansfield, MC	Facility:	
Dept/Sec: Dept Medicine	Assoc Investigators	
Key Words: Cromolyn; Nonspecific bronchial hyperreactivity		
Accumulative MEDCASE Cost	Est OMA Cost:	Periodic Review Results
Study Objective:		

To investigate whether cromolyn by inhalation will modify histamine induced nonspecific bronchial hyperreactivity.

## Technical Approach:

Twenty adult non-pregnant asthmatic patients with the history of seasonal asthma present in the spring and the late summer will be chosen for entry into this study. Each institution will contribute 20 subjects for a grand total of 80 participants. The subjects would not have received any allergen immunotherapy for at least one year prior to entering into the study. To be eligible for the study, they will have 3+, 4+ prick puncture skin test to the relevant spring and fall aeroallergens in the locality of the participating institution. The patients would have had a history of asthma management suggesting that they can be comfortable with "as needed" bronchodilator medication.

The study will commence on or about 1 Jan 83. During the subject's first visit in January 1983, they will undergo a histamine bronchial challenge. This will be considered baseline histamine reactivity. The patient, during this visit will be instructed in the proper use of cromolyn through a spinhaler. They then will return on or about the 1st of February 1983 to receive a spinhaler and a packet which contains either cromolyn or a similar appearing placebo. We will use this on a four-times daily basis and record such usage. They will also record the use of any other "as needed" medication to treat their asthma. The patients will perform three peakflow measurements in the morning, dinner time, and at bedtime. They will record the best peakflow at each of the time frames. At the end of the day, using a daily symptoms score sheet, they will record their

symptoms and medication used on the score sheet. During each week of the study, the subjects will be contacted by a member of the staff of the allergy-immunology service conducting the study. This will be a telephonic conversation to discuss their progress with the medication, their understanding of the symptoms score sheets and data recording, and to maintain their continued compliance with the study. The patients will return to the participating allergy-immunology service at 2 months, 4 months, and 6 months after commencing treatment. During each of these visits, a repeat histamine bronchial challenge will be performed. During the study period itself, if the subject should have an exacerbation of their asthma, they will be seen as soon as humanly possible by one of the principal investigators from their participating allergy-immunology service. They will be encouraged to utilize this route of care rather than emergency room or primary care unit treatment so that adequate documentation, including pulmonary functions of any acute episode, will be available for future evaluation. At the end of the 6 months of treatment, the symptom medication score sheets, the daily peakflow measurements, and the change in bronchial responses to histamine over the course of time will be compared between the placebo and the active treatment group. Statistical analysis will be by both parameteric and nonparametric means as appropriate.

**Progress:**

This protocol was approved late in FY82 and has not begun.

# Detail Summary Sheet

Date: 1 Oct 82 Prot No: 82/51 Status: Ongoing

## Title:

The Effect of Ketotifen (Zaditen) on Immunologic Pharmacologic Skin Test Reactions

Start Date:

Est Comp Date:

Principal Investigator:

Facility:

LTC L.E. Mansfield, MC

Dept/Sec: Dept Medicine

Assoc Investigators

Key Words:

Ketotifen; Skin reaction

Accumulative MEDCASE

Est

Periodic

Cost

OMA Cost:

Review Results

Study Objective:

To investigate whether orally administered Ketotifen (Zaditen) will modify allergen induced skin reactions.

## Technical Approach:

Twenty adult male allergic individuals with a positive skin test to either Russian thistle or Bermuda grass will be entered into this study. These patients will have highly reactive skin tests; at least a 4+ prick skin test to one to 20 glycerinated extract of Bermuda grass or Russian thistle pollen. The study will be conducted when the pollen to which they are allergic is not present in the atmosphere of El Paso. After the initial screening skin test, further skin tests of the subjects will be done with specifically prepared material reconstituted from freeze dried extracts on weekly basis. All skin testing will be done in the titrated prick skin test method on the patient's back. All the pharmacologic agents will be reconstituted likewise each week. The protocol will be performed in two phases: Phase I - the subjects will return to the clinic after having been off any antihistamine for five days. A detailed skin testing will be performed to include testing to the relevant allergen at two-fold dilution from one to twenty to one to 2560 dilutions; doubling dilutions of codeine beginning with 10 mg per ml concentration and histamine in two-fold dilutions beginning with one mg per ml concentration. The last dilution that is capable of eliciting a 3 mm wheal will be considered the lowest responding dilution. The size of the erythema will be measured and also recorded in each subject; the subject will then be entered into either Group A or B in a random fashion. The patients in Group A will receive Ketotifen 1 mg daily for three days with a 1 mg dose on the fourth day when repeat testing will be

performed. Group B will receive 3 days identical looking placebo, but on the fourth day will receive 1 mg of Ketotifen. Skin testing will be repeated in the same fashion as described for the baseline. Then patient will also return at 2, 4, 6, and 8 days while taking no further medication and have this skin testing repeated. The results at each testing time will be compared to the baseline to ascertain: 1) the effects of the varying treatment and 2) the duration of carryover effect if any.

After this information is available, Phase II of the study will begin. In Phase II of the study, the same volunteer subjects, or a similar group, will be chosen. The criteria for entry will be the same, if new volunteers are added to the study. These patients will have titrated prick skin tests performed to establish a baseline. They will take one of the following regimens of Ketotifen in a random blinded fashion. Each patient will receive four capsules twice a day for three days and two capsules on the day of the testing. The capsules in various combinations will contain either 1 mg Ketotifen or placebo. During this three day trial, subjects will receive 1 mg Ketotifen, 2 mg Ketotifen, 3 mg Ketotifen, or 4 mg Ketotifen daily dose. All skin testing will be done at 0800 in the morning in consideration of the recognized circadian variation in skin reactivity. Each volunteer will serve as his own control for analysis in this study. Each volunteer will be tested while on each medication regimen. The skin testing results at varying doses will be compared to see if there is increasing medication effect with greater doses. At the time of the testing, the patient will also be queried as to side effects of the regimen. An IND number has been submitted by the Sandoz Corp for the use of this drug. Skin test responses will also be cellophane tape transferred to paper and measured with a compensating polarized planimeter. Statistical analyses of this skin testing at each time frame will be by parametric and nonparametric methods.

#### Progress:

This protocol was approved late in FY82 and has not begun.

### Detail Summary Sheet

Date: 1 Oct 82	Prot No: 82/52	Status: Ongoing
Title: Usage of Sus-Phrine in Control of Allergic Skin Reaction		
Start Date:	Est Comp Date:	
Principal Investigator: MAJ S. Ting, MC	Facility:	
Dept/Sec: Dept Medicine	Assoc Investigators	
Key Words:		

Sus-phrine; Skin reaction

Accumulative MEDCASE	Est	Periodic
Cost	OMA Cost:	Review Results
Study Objective:		

To determine duration of action of sus-phrine in inhibiting allergen induced skin reaction.

#### Technical Approach:

Twenty adult volunteers from the Allergy Clinic with no contraindications to adrenergic therapy.

Skin testing will be performed with an allergen to which a given subject has been shown to be reactive by previous routine skin test, and with 48/80 (mast cell degranulator), codeine, histamine, and sus-phrine.

#### Skin testing procedure:

- Skin prick test with predetermined allergen (e.g., ragweed) 1:20
- Skin prick test with 48/80 100 mg/ml
- Skin prick test with codeine 1.0%
- Skin prick test with histamine 1 mg/ml

After 15 minutes record size of wheal and flare reaction. Subcutaneously inject .15 ml of 1:200 sus-phrine. At fifteen minutes, 1, 2, 4, 6, and 8 hours post sus-phrine injection, repeat.

#### Progress:

This protocol was approved late in FY82 and has not begun.



# Detail Summary Sheet

Date: 1 Oct 82      Prot No: 82/53      Status: Ongoing

## Title:

Efficacy Trial Using Cyproheptadine and Cimetidine for Pruritus in Polycythemia Vera PVSG-15

Start Date:

Est Comp Date:

Principal Investigator:

Facility:

COL Ray O. Lundy, MC

Dept/Sec:      Dept Medicine

Assoc Investigators

Key Words:

H<sub>1</sub> and H<sub>2</sub> blocking agents; Pruritus

Accumulative MEDCASE  
Cost

Est  
OMA Cost:

Periodic  
Review Results

Study Objective:

The aim of this study is to determine whether H<sub>1</sub> and H<sub>2</sub> blocking agents used concomitantly are efficacious in alleviating the pruritus of polycythemia vera. All patients currently on active protocols (PVS-01,05,08) will NOT be eligible. Should usefulness be established, a randomized trial will be considered.

Technical Approach:

The details are lengthy and specified in the Polycythemia Vera Study Group protocol. Duplicates are kept on file in the Department of Clinical Investigation and are available upon request.

Progress:

This is a new protocol approved in the last month of FY82.

# Detail Summary Sheet

Date: 1 Oct 82      Prot No: 82/54      Status: Ongoing

## Title:

Study of the Clinical Features and Natural History of Asymptomatic Patients with Myeloproliferative Disorders PVSG-13

Start Date:

Est Comp Date:

Principal Investigator:

Facility:

COL Ray O. Lundy, MC

Dept/Sec: Dept Medicine

Assoc Investigators

Key Words:

Myeloproliferative disorders

Accumulative MEDCASE

Est

Periodic

Cost

OMA Cost:

Review Results

Study Objective:

To obtain a clinical and laboratory data base on patients with myeloproliferative disorders prior to the time they require treatment under other MPD protocols.

To define the natural course of the disease as to the development of: a) splenomegaly; b) progressive fibrosis; c) leukemic conversion; d) thromboembolic complications and e) other neoplasm.

To demonstrate the development of cytogenic and pathologic abnormalities in bone marrow and peripheral blood.

To establish predictors of a more symptomatic stage of the disease.

Technical Approach:

The details are lengthy and specified in the Polycythemia Vera Study Group protocol. Duplicates are kept on file in the Department of Clinical Investigation and are available upon request.

Progress:

This is a new protocol approved in the last month of FY82.

# Detail Summary Sheet

Date: 1 Oct 82 Prot No: 82/55 Status: Ongoing

## Title:

Efficacy Trial Using Hydroxyurea (HU) in Thrombocytosis PVSG-12

Start Date:

Est Comp Date:

Principal Investigator:

Facility:

COL Ray O. Lundy, MC

Dept/Sec:

Assoc Investigators

Key Words:

Hydroxyurea; Thrombocytosis

Accumulative MEDCASE

Est

Periodic

Cost

OMA Cost:

Review Results

Study Objective:

Despite the fact that a number of alkylating agents have been shown to be effective in the treatment of primary thrombocytosis, the known chemogenic and carcinogenic effects of these drugs prohibit their use in young males and females. It is, therefore, of paramount importance to find an agent which will be effective in the treatment of this disease in all age groups, but which might eventually be specifically useful in the treatment of the younger age groups.

The aim of this study is to evaluate the efficacy of HU (a non-mutagenic, noncarcinogenic agent) in preventing and controlling the symptoms of thrombosis and bleeding with 1) the clinical entity primary thrombocythemia, 2) those patients with myelofibrosis-myeloid metaplasia with elevated platelet counts, 3) those patients with unclassified myeloproliferative disease with elevated platelet counts.

Technical Approach:

The details are lengthy and specified in the Polycythemia Vera Study Group protocol. Duplicates are kept on file in the Department of Clinical Investigation and are available upon request.

Progress:

This is a new protocol approved in the last month of FY82.

Detail Summary Sheet

Date: 1 Oct 82 Prot No: 82/63 Status: Ongoing

Title:

Effects of Beta-2 Agonist on Codeine 48/80 Induced Skin Reaction

Start Date:

Est Comp Date:

Principal Investigator:

Facility:

MAJ S. Ting, MC

Dept/Sec: Dept Medicine

Assoc Investigators

Key Words:

B-2 agonist; Skin reaction

Accumulative MEDCASE

Est

Periodic

Cost

OMA Cost:

Review Results

Study Objective:

To determine whether locally applied B<sub>2</sub> agonist suppresses the histamine release induced by codeine and 48/80 in human allergic skin reactions.

Technical Approach:

Ten adult volunteers will be selected from the Allergy Clinic. Skin testing will be performed with codeine 1%, 48/80, 10 mg/ml and terbutaline

Skin testing injections:

0.02 ml of 1% codeine or 1% 48/80

0.02 ml of PBS PNU/cc

0.02 ml of 1% codeine and terbutaline 2 ug/ml

0.02 ml of terbutaline 2 mg/ml (final concentration).

Wait fifteen minutes and record the size of the wheals and flares. Proceed to skin blister technique for measurement of histamine release.

Progress:

This is a new protocol approved in the last month of FY82.

### Detail Summary Sheet

Date: 1 Oct 82      Prot No: 82/64      Status: Ongoing

Title:  
Effects of Propranolol on Terbutaline Suppression of Allergic Skin Reaction

Start Date:      Est Comp Date:  
Principal Investigator:      Facility:  
MAJ S. Ting, MC

Dept/Sec: Dept Medicine      Assoc Investigators  
Key Words:  
Propranolol; Terbutaline; Skin reactions

Accumulative MEDCASE      Est      Periodic  
Cost      OMA Cost:      Review Results  
Study Objective:

To determine whether locally applied propranolol inhibits terbutaline suppression of histamine release in human allergic skin reaction

#### Technical Approach:

Twenty adult patients will be selected on the basis of a 4+ positive prick skin test to ragweed allergen from the Allergy Clinic. Skin testing will be performed with ragweed, terbutaline and propranolol.

#### Skin testing injections:

0.02 ml of ragweed 1000 PNU/cc  
0.02 ml of ragweed 1000 PNU/cc and 0.02 ml of terbutaline 2 ug/ml.  
0.02 ml of ragweed 1000 PNU/cc and 0.02 ml of terbutaline and propranolol 2 ug/ml (FC).  
0.02 ml of PBS

Wait fifteen minutes and record sizes of the wheals and flares. Proceed to skin blister technique for the measurement of histamine release.

#### Progress:

This is a new protocol approved the last month of FY82.

Detail Summary Sheet

Date: 1 Oct 82      Prot No: 81/27      Status: Terminated  
Title:  
Effect of Reassessment on Deterioration of Diabetic Patients'  
Knowledge and Management Skills, and on Compliance.

Start Date:      Est Comp Date:  
Principal Investigator:      Facility:

MAJ J.R. Bonnell, ANC

Dept/Sec:      Dept Nursing      Assoc Investigators  
Key Words:

Diabetes mellitus

Accumulative MEDCASE      Est      Periodic  
Cost      OMA Cost:      Review Results  
Study Objective:

To determine if frequent reassessment at one month, three months, six months intervals improves diabetic patients' knowledge and management skills and compliance.

Technical Approach:

Two groups of adult diabetic patients, ages 18-70, will be randomly selected from the total diabetic population of a large military medical center, and assigned randomly to either a control group or an experimental group. Both groups will be given identical instruction on diabetic management skills and diabetic information. The checklists will be maintained in a file and updated appropriately.

Patients in both groups will need to have correct performance of at least five objectives one week after the initial teaching has been done in order to qualify for entry into the study. Patients in the experimental group will require reassessment at one month, three months, and six months intervals. Patients in the control group will require reassessment at six month intervals, with no intervening assessment. Additional factors that will be collected include: age, duration of diabetes, previous attendance at formal diabetes teaching sessions such as classes.

Progress:

None reported.

# Detail Summary Sheet

Date: 1 Oct 82 Prot No: 81/60 Status: Completed

Title:  
Hemolysis During Blood Administration

Start Date: Est Comp Date:

Principal Investigator: Facility:

COL E. Sullivan, ANC

Dept/Sec: Dept Nursing Assoc Investigators

Key Words:

Hemolysis

Accumulative MEDCASE	Est	Periodic
Cost	OMA Cost:	Review Results

Study Objective:

To determine whether patients are receiving effective hemotherapy during blood administration. Determining if there is significant hemolysis may account for a patient's decreased response to blood therapy in the absence of detectable antibodies or stress related factors. Assumptions have been made regarding the size of the red blood cell and the diameter of the bore of different gauge needles for safe passage of red blood cells. Hemolysis has not been measured to assure the assumptions are valid using the current, improved equipment, recommended time(s) necessary for safe infusion, or with the different types of blood components in use today.

Technical Approach:

The needles will be selected randomly from the container in which they arrive. The independent variables - type and gauge of the needle, use of filters, rate of infusion and type of blood products - will be actively manipulated to determine their effect on hemolysis, the dependent variable.

Twenty-thirty patients with leukemia will be selected for the study of platelet therapy, to minimize the bias of the disease process. The temperature of the infused platelets will be recorded as will the patient's history. Sixty patients from the MICU, SICU and Trauma Unit requiring whole blood transfusions will be studied as they appear and randomly compared, if possible, to similar patients who did not require transfusion. Sixty patients from the MICU, SICU and Trauma Unit requiring packaged red blood cells will also be

studied.

The Spielberger State and Trait Anxiety Tests will be used to measure the patients trait (normal) anxiety and the patients state anxiety that was experienced during and following blood administration. Permission was granted for the use of the STAI Form X-1 and X-2 by Dr Charles Spielberger.

Progress:

Data collection is complete. The results will be collected and submitted by the associate investigator, Candice Meade, in partial fulfillment for the Master of Science degree in Nursing at the University of Texas at El Paso.



# Detail Summary Sheet

Date: 1 Oct 82      Prot No: 82/29      Status: Completed

## Title:

Impact of Intraoperative Hypnoidal Intervention on Postoperative Anxiety Levels

Start Date:

Est Comp Date:

Principal Investigator:

Facility:

CPT M. Jacobs, ANC

Dept/Sec: Dept Nursing

Assoc Investigators

Key Words:

Hypnoidal intervention; Postoperative anxiety

Accumulative MEDCASE  
Cost

Est  
OMA Cost:

Periodic  
Review Results

Study Objective:

To measure the effectiveness of intraoperative hypnoidal intervention in decreasing postoperative anxiety levels.

## Technical Approach:

This study is designed to measure the effectiveness of intraoperative hypnoidal intervention by assessing subjects' preoperative and postoperative anxiety levels using the State-Trait Anxiety Inventory (STAI) developed by Charles D. Spielberger and associates in the mid-1960s. The STAI consists of two separate self-report inventories geared to measure two distinct concepts of anxiety: state anxiety and trait anxiety.

State anxiety is considered a transitory condition of perceived tension. Thus, the anxiety state (A-State) scale of the inventory is construed to assess how the subject feels right at the moment when the test is being taken.

Trait anxiety represents a relatively stable condition of anxiety proneness. The trait anxiety (A-Trait) portion of the instrument measures how the individual feels generally.

For this research study, the A-State scale of Speilberger's inventory will be used exclusively to gauge an individual's response to the psychological stresses specifically engendered by surgery. The A-State scale consists of 20 statements which require the subject to react according to his feelings at that particular moment. The test is self-administered and takes approximately 10-20 minutes to complete. Retests with this instrument take only about 5 minutes. The reliability and validity of the STAI were thoroughly investigated during its development. Currently, the STAI is deemed one of the best standardized measures of anxiety.

Subjects will be selected as availability permits. One group will receive ~~hypnoidal~~ hypnoidal intervention intraoperatively while the other will function as a control. Ideally each group will contain approximately 20 individuals.

#### Progress:

A nonequivalent control group quasi-experimental research design was employed. Subjects were selected as availability permitted and were randomly assigned to one of two groups. One group received hypnoidal intervention intraoperatively while the other functioned as a control. Each group contained six individuals.

Those patients who met appropriate criteria were invited by the investigator to participate in the study. If the individual acquiesced, informed consent was obtained.

The afternoon of the day before surgery the A-State portion of the STAI was administered to all subjects. The researcher remained with the individual throughout the test in order to answer any questions.

Actual hypnoidal intervention began as soon as those patients in the experimental group entered the operating room. Prior to induction, relaxation techniques and imagery were employed. The researcher continued speaking softly to the patient, as he was being prepared for anesthesia.

Throughout the surgery the researcher continued to communicate with the subject to keep him abreast of the progress of the operation, position changes, or any unusual surgical manipulation. Patients in the control group received routine anesthetic care during their surgery. Neither suggestion nor any other type of hypnoidal intervention were used.

On the afternoon of the first postoperative day the STAI A-State test was readministered to patients in both the control and experimental groups. Testing procedures were identical to those for the pretest. All testing and hypnoidal intervention were done by a single investigator trained in the use of hypnosis.

The two independent sample problem was used as the basis of data analysis in order to determine if the mean test score of the experimental group differed significantly ( $\alpha = 0.05$ ) from the mean value of the control group.

Several calculations are necessary when doing a two-independent sample problem. A standard deviation was computed for each group based on the postoperative STAI A-State scores. Subsequently an F-test was done to determine if the two standard deviations were equivalent. As this was the case, a pooled standard deviation was estimated in order to facilitate testing the equality of the two population means.

Because of the small sample size, a bell-shaped or normal distribution was assumed. Accordingly a t-test was used to decide if the two population means were equivalent. An alpha value of 0.05 was considered significant.

Seven females and five males participated in the study. Individuals were from 24 to 62 years of age and all had a history of at least one previous general anesthetic. Seven patients were ASA category I and the remainin five were ASA category II. Individuals underwent a variety of relatively common elective procedures which were either orthopedic, gynecological, or general surgical in nature. All subjects cooperated readily with the investigator and none withdrew from the study while it was in progress.

Postoperative STAI A-State scores were computed for both the control and experimental groups. A mean value of 34 was found for the experimental group with a standard deviation of 7.88. The mean for the control group was 44 with a standard deviation of 5.32.

Because the two independent sample problem served as the framework for analysis, an F-test was done initially to determine if the two standard deviations were equivalent. Finding this to be the case, a pooled estimate of the two standard deviations was calculated in order to test the equality of the two population means ( $s_p = 6.72$ ).

Two hypothesis were tested:

$$H_0: M_x = M_y$$

$$H_A: M_x \neq M_y$$

A one-tailed t-test with an alpha value of 0.05 and 10 degrees of freedom was done. The computed t-value of -2.5 was less than the critical t-value of -1.8; therefore, the null hypothesis was rejected.

As a result of statistical analysis, the alternative hypothesis was accepted. Thus, the postoperative anxiety levels of patients who received intraoperative hypnoidal intervention were significantly lower ( $\alpha = 0.05$ ) than the postoperative anxiety levels of patients who received conventional anesthetic management.

Recommendations for further study: Reproducing this study with a larger sample would enable one to assess with more certainty the effects of intraoperative hypnoidal interven on. The impact of intraoperative hypnoidal intervention may be evaluated using another standard tool of anxiety measurement (e.g., the IPAT Anxiety Scale, the Taylor Manifest Anxiety Scale, or Zuckerman's Affective Adjective Checklist).

Parameters other than anxiety level (e.g., narcotic use, length of hospital stay) may be used to judge the efficacy of intraoperative hypnoidal intervention. If a pen and paper test is done postoperatively to assess anxiety, retesting on the second and third postoperative day as well as on the day immediately following surgery may provide fresh insights.

# Detail Summary Sheet

Date: 1 Oct 82 Prot No: 82/30 Status: Completed

## Title:

The Relationship Between Maximum Inspiratory Force (MIF) and Response to Tetanic Stimulation in Patients Following Nondepolarizing Blockade Reversal

Start Date:

Est Comp Date:

Principal Investigator:

Facility:

CPT Craig Allen, ANC

Dept/Sec: Dept Nursing

Assoc Investigators

## Key Words:

MIF; Tetanic stimulation; Neuromuscular blockade reversal

Accumulative MEDCASE

Est

Periodic

Cost

OMA Cost:

Review Results

## Study Objective:

To determine if there is a correlation between the MIF and the response to tetanic stimulation of fifty hertz for five seconds in patients who have had a nondepolarizing neuromuscular blocker that has been reversed.

## Technical Approach:

The sample population will be at least fifty adults, both military and civilian, who do not have any neuromuscular disease and who are having N<sub>2</sub>O, narcotics and nondepolarizing blocker anesthesia. The patients will be in ASA categories 1 and 2 only. The patients will be having abdominal perineal or extremity surgery, in the supine or lithotomy position. Patients having thoracic procedures will be excluded. Each patient will be required to sign a consent form to be eligible. At the end of the surgical procedure neuromuscular blockade will be reversed with Prostigmine and Robinul. Three minutes after reversal, a tetanic stimulation of 50 hertz will be delivered via a peripheral nerve stimulator to a pad placed on the wrist, over the ulnar nerve. The response to stimulation will be timed for a maximum of five seconds; timing will stop if fade of tetanus is observed. Immediately after tetanic stimulation a measurement of MIF in cm of H<sub>2</sub>O will be taken. The responses will be recorded. Data analysis will be done statistically using the Pearson R coefficient of correlation.

### Progress:

The population studied consisted of 25 adult patients. Age ranged between 18 and 55 years with a mean age of 27.84 years. The population included 16 females and 9 males, all ASA Category I and II. All subjects met prestudy criteria. All surgical procedures were performed on extremities or on the lower abdomen. The surgical procedures involved included ten bilateral tubal ligations, four abdominal hysterectomies, two cesarean sections, seven arthroscopies, and arthrotomies of the knee, and two appendectomies.

The results of MIF and sustained tetanic response were statistically analyzed using the Pearson's R Coefficient of Correlation. An R value of 0.537 was obtained.

The Student's t-test was applied to the results, and were found to be statistically significant at the .01 level ( $P < .01$ ). A  $R^2$  value of .288 was obtained; therefore, 28.8% of the total variation in MIF could be accounted for by its linear relationship with sustained tetanic response.

The objective of this study was to determine if there is a correlation between MIF and the response to a 50 hz sustained tetanic stimulation. The investigators wanted to expand on criteria used to determine when a patient could be extubated following nondepolarizing neuromuscular blockade reversal. The study showed a small linear relationship. However study of the scatter diagram reveals that in every instance where a five second tetanic response was obtained, the corresponding MIF value was equal to or in excess of -25cm H<sub>2</sub>O.

The research design contained inherent limitations. The subject sample was selected by convenience which tends to limit generalization. The population size was small, which also limited general applicability. Timing of tetanic response ceased at five seconds: it is possible that a stronger linear relationship could have been demonstrated statistically if response times were increased. The literature, however, shows the five second response time to be adequate.

The study was pre-experimental and the investigators were interested in a clinically feasible testing tool. Further investigation into ventilatory function and neuromuscular blockade reversal is warranted.

The use of conventional criteria for extubation (i.e., head lift, tidal volume, vital capacity, and MIF) should continue to be utilized. The addition of the peripheral nerve stimulator and measurement of sustained tetanic response may be a useful adjunct and warrants further study.

Detail Summary Sheet

Date: 1 Oct 82 Prot No: 77/02 Status: Terminated

Title:

Ultrastructural Investigation of Prostaglandins and Their Precursors  
in the Human Fetal Chorioamnionic Membrane

Start Date:

Est Comp Date:

Principal Investigator:

Facility:

B.E.F. Reimann, PhD, DAC

Dept/Sec: Obstetrics-Gynecology

Assoc Investigators

Key Words:

Prostaglandins; Chorioamnion

Accumulative MEDCASE

Est

Periodic

Cost

OMA Cost: \$0 (740)

Review Results

Study Objective:

To determine if prostaglandins and their precursors can be localized  
in fetal membrane and to detect any change with these in association  
with labor.

Technical Approach:

Using indirect antibody labeling technique, prostaglandins were  
tagged at a cellular level. The section was then imbedded and  
ultrathin sections made.

Progress:

Technical support for research electromicroscopy continues to be  
unavailable.

Detail Summary Sheet

Date: 1 Oct 82 Prot No: 77/06 Status: Completed

Title:

Study to Determine the Ability of Amniotic Fluid to Inhibit Growth of E. Coli

Start Date:

Est Comp Date:

Principal Investigator:

Facility:

COL David Boyce, MC

Dept/Sec: Obstetrics-Gynecology

Assoc Investigators

Key Words:

Amniotic fluid; Bacterial growth inhibition

Accumulative MEDCASE

Est

Periodic

Cost

OMA Cost: 0(6524)

Review Results

Study Objective:

To devise an improved laboratory method for determining the inhibitory property of amniotic fluid.

Technical Approach:

The growth and/or inhibition of a laboratory strain of E. Coli in amniotic fluid as well as certain controlled media is to be monitored by a technique using C14 tagged glucose in the various culture media and monitored by the amount of 14 CO2 eluted as measured in a liquid scintillation counter. Maternal and cord blood serum zinc levels will be determined as well as the zinc and phosphate ratios of the amniotic fluid. An attempt will be made to correlate the inhibitory or noninhibitory effect of amniotic fluid on the E. coli as well as the zinc and zinc/phosphate ratios of this inhibitor effect to neonatal sepsis.

Progress:

Attempts to isolate and identify an inhibitory peptide have been unsuccessful. Previous reports have detailed the data and presentations from this study.



# Detail Summary Sheet

Date: 1 Oct 82 Prot No: 77/25 Status: Ongoing

## Title:

A Comparison of Phospholipid Levels and Choline Phosphotransferase (CPT) Activity in Amniotic Fluid and Newborn Tracheal Fluid

Start Date:

Est Comp Date:

Principal Investigator:

Facility:

LTC F. Theard, MC

Dept/Sec: Obstetrics-Gynecology

Assoc Investigators

Key Words:

Phosphatidylglycerol; Amniotic fluid

COL L.L. Penney, MC

David O. Rauls, PhD, DAC

Accumulative MEDCASE

Est

Periodic

Cost

OMA Cost:\$200(6111)

Review Results

Study Objective:

To determine if the level of phosphatidyl glycerol (PG) and phosphatidyl inositol (PI) or the activity of choline phosphotransferase could serve as an accurate index of lung maturity.

Technical Approach:

Amniotic fluid, and neonatal gastric and pharyngeal fluids which are normally discarded, will be analyzed for phosphatidyl glycerol, phosphatidyl inositol, choline phosphotransferase, and magnesium. The levels measured will be correlated with the incidence and severity of neonatal respiratory stress and hyaline membrane disease.

Progress:

A rapid analysis for PG in amniotic fluid has been developed and is being evaluated for clinical applicability. The technique is being presented Dec 82 at the American Chemistry Society Regional Meeting (see FY83 report). Accumulation of patients has slowed as the number of amniocenteses being performed diminishes, but clinical correlations to date have been as expected.

# Detail Summary Sheet

Date: 1 Oct 82	Prot No: 80/9	Status: Completed
Title: Effect of Terbutaline on Surface Active Phospholipids in Adult and Fetal Lung		
Start Date:	Est Comp Date:	
Principal Investigator: D.O. Rauls, PhD, DAC	Facility:	
Dept/Sec: Obstetrics-Gynecology	Assoc Investigators	
Key Words: Terbutaline; Surface active phospholipids		
Accumulative MEDCASE	Est	Periodic
Cost	OMA Cost: \$0 (1040)	Review Results
Study Objective:		

To determine if administration of Terbutaline affects lung maturation profile in adult dog and fetal rabbit lungs.

## Technical Approach:

Anesthetized adult beagle dogs will be studied in the first phase of the project. They will be given .5 mgm Terbutaline or placebo in 250 cc of saline over a two-hour period. Tracheal bronchial washings using saline will be done at zero, two, four, and six hours and the washings saved and analyzed for surface active phospholipid content to determine if acute infusion of Terbutaline has affected the phospholipid content in the lungs. In phase two, pregnant rabbits with immature fetuses will be given Terbutaline or a placebo subcutaneously over a 3-day period. The animals will then be sacrificed and the fetal and adult lungs will be studied for surface active phospholipids to determine if a change has occurred.

## Progress:

The effect of the beta-2-adrenergic receptor agonist terbutaline on the phospholipid composition of anesthetized adult beagle dog tracheal wash was studied. Adult beagle dogs were anesthetized with sodium pentobarbital and administered either 0.9% saline or 0.5 mg of terbutaline in 250 ml of 0.9% saline over a two hour period. A pulmonary lavage was performed with 50 ml of 0.9% saline and the phospholipid composition of the lavagate was determined. Percent composition data revealed little effect of the drug on surfactant composition. Calculation of phosphatidylcholine/sphingomyelin (L/S) ratios revealed a significant ( $p < 0.05$ ) decrease in the L/S ratio one hour after terbutaline administration. The results indicated that when studying the effects of drugs on pulmonary surfactant quality one must consider the effects on the entire spectrum of phospholipids present rather than on phosphatidylcholine alone. Six additional dogs were studied in an attempt to substantiate the reported results.(AFD-ACOG, 13-18 Oct 81, Phoenix, AZ). This material has been partially analyzed and will be combined with data from protocol 81/49 in next year's report.

# Detail Summary Sheet

Date: 1 Oct 82 Prot No: 80/17 Status: Completed

## Title:

Transvaginal Absorption of Estrogens in Patients Following Pelvic Irradiation

Start Date:

Est Comp Date:

Principal Investigator:

Facility:

MAJ H. Greenberg, MC

Dept/Sec: Obstetrics-Gynecology

Assoc Investigators

Key Words:

Estradiol; Estrone

COL L.L. Penney, MC

Accumulative MEDCASE

Est

Periodic

Cost

OMA Cost: \$640(2730)

Review Results

Study Objective:

To quantitate serum levels of 17 $\beta$ -estradiol and estrone following vaginal application of the appropriate cream in patients who are post-irradiation of the vaginal epithelium.

## Technical Approach:

Patient volunteers who have received pelvic irradiation for nonestrogen dependent neoplasms will be studied. All estrogen medications will be withdrawn for four weeks. Eight to ten patients will be divided into two groups randomly. One group will receive Premarin 1.25 mg and the other Estrace 2 mg intravaginally. Baseline serum estrone and estradiol concentrations will be obtained and repeated at 30 minutes and at one hour, two hours, four hours, eight hours, and 24 hours following the medication. One week later the groups will be reversed. Insofar as possible, patients will be matched regarding age, diagnosis and amount of irradiation received.

## Progress:

Serum concentrations of unconjugated estrone(E<sub>1</sub> and 17 $\beta$ -estradiol(E<sub>2</sub>) have been measured in patients before and after 1.25 mg of conjugated estrogens(Premarin<sup>R</sup>) administered intravaginally. The measurements were repeated using 2 mg of micronized estradiol (Estrace<sup>R</sup>) administered intravaginally one week later to six of the women and seven months later in one. All the patients had completed a full course of irradiation for pelvic malignancy. Baseline, 1/2, 1,2,4,8 and 24 hour samples were analyzed. After conjugated estrogens mean serum E<sub>2</sub> increased

11-fold to peak at 353 pg/ml at one hour while  $E_1$  increased 3.1-fold to peak at 239 pg/ml at two hours. After micronized  $E_2$  mean serum  $E_2$  increased 111.6-fold to peak at 1339 pg/ml at one hour while  $E_1$  increased 3.3-fold to peak at 411 pg/ml at two hours. These data are the first in irradiated women. Compared to literature values in normal untreated postmenopausal patients they demonstrated 1) more rapid absorption with both preparations 2) higher serum concentrations of both estrogens with both preparations (except for one report) 3) an increase  $E_2/E_1$  ratio following conjugated estrogens and 4) rapid decline in  $E_2$  concentrations, but less so with  $E_1$ , similar to normal women. This suggests even less direct tissue uptake by the irradiated mucosal cells themselves than in non-irradiated atrophic vagina or intrinsic changes in the cell membranes. Protocols are being written to ascertain if continued exposure to estrogen will impede vaginal absorption as it does in nonirradiated mucosa.

# Detail Summary Sheet

Date: 1 Oct 82      Prot No: 80/25      Status: Ongoing

## Title:

Placental Levels of 5a-dihydroprogesterone in Normal Pregnancy and Those Complicated by Pre-eclampsia

Start Date:

Est Comp Date:

Principal Investigator:

Facility:

David O. Rauls, PhD, DAC

Dept/Sec: Obstetrics-Gynecology

Assoc Investigators

## Key Words:

Dihydroprogesterone; Pre-eclampsia

LTC F. Theard, MC

Accumulative MEDCASE

Est

Periodic

Cost \$6,603

OMA Cost:\$0 (345)

Review Results

## Study Objective:

To determine if placentas of pregnancies complicated by pre-eclampsia have a different concentration of 5a-dihydroprogesterone then those of uncomplicated pregnancies.

## Technical Approach:

Placentas from normal and pregnancies complicated by pre-eclampsia will be studied for their content of 5a-dihydroprogesterone. After consent has been obtained from patients who are admitted in labor, the placentas obtained at birth will be drained of blood and the membranes excised. They will then be weighed and, using the mass-spectrometer, presence and concentrations of 5a-dihydroprogesterone will be determined. Concentration of 5a-dihydroprogesterone in pregnancies complicated by pre-eclampsia will be compared to that of normal pregnancies. Twenty patients in each group will be studied initially and the mean levels of 5a-dihydroprogesterone will be compared by Student's t-test.

## Progress:

Personnel constraints have prohibited work on this protocol. Tissue is expected to be collected, with the aid of the new associate investigator, in FY83.

Detail Summary Sheet

Date: 1 Oct 82 Prot No: 81/03 Status: Ongoing

Title:

Serial Measurement of Serum, Zinc, Magnesium, Copper, Lead, Lithium and Arsenic During Pregnancy.

Start Date:

Est Comp Date:

Principal Investigator:

Facility:

LTC R.W. Cotterill, MC

Dept/Sec: Obstetrics-Gynecology

Assoc Investigators

Key Words:

Trace elements

Accumulative MEDCASE

Est

Periodic

Cost

OMA Cost: \$417(1898)

Review Results

Study Objective:

To determine the serum levels of certain trace elements during each trimester of pregnancy in patients from the El Paso area. Specific goals will include: (1) Comparison of the serum levels of trace elements in two populations of patients, first the U.S. Army dependent population; second the native population of Thomason General Hospital. (2) To establish normal mean levels of zinc, magnesium, copper, lead, lithium, and arsenic at various stages of pregnancy. (3) To suggest future studies correlating the findings of serum levels of trace elements with pregnancy outcome.

Technical Approach:

The plan will be to determine the serum levels of copper, zinc, magnesium, lithium, lead and arsenic during the first trimester, again at 20 weeks gestation, and at term. In addition, fetal levels as determined by cord blood at delivery will be obtained. These values will be compared with nonpregnant controls.

Two separate patient populations will be compared, those of William Beaumont Army Medical Center and those of R.E. Thomason General Hospital. The two populations may reflect different levels of environmental exposure to these trace elements, as well as a possible difference in dietary intake.

a. The study would include approximately 50 pregnant patients from the OB Service, WBAMC, and a similar number of patients from the El Paso County population of RETGH.

b. Controls would be nonpregnant females of similar ages.

c. The investigation would include sampling of 10 cc vacutainer at the following intervals during pregnancy: 1st trimester, mid-trimester, time of labor and delivery, and cord blood at delivery.

d. Sampling of controls at one time.

e. A questionnaire stating the historical data pertinent to each patient will be distributed. This will request the information regarding birth place, location of residence, and employment.

f. Additional control - the studied pregnant patients will be tested at six to 12 weeks postpartum.

**Progress:**

Sampling is completed and trace element analysis is nearing completion. The data will be analyzed in FY83.

Detail Summary Sheet

Date: 1 Oct 82 Prot No: 81/44 Status: Ongoing

Title:

Effect of Intravenous Terbutaline on Phospholipid Content of Adult Dog Lungs

Start Date:

Est Comp Date:

Principal Investigator:

Facility:

LTC R.W. Cottrill, MC

Dept/Sec: Obstetrics-Gynecology

Assoc Investigators

Key Words:

Terbutaline; Surface active phospholipids

Accumulative MEDCASE

Est

Periodic

Cost

OMA Cost:

Review Results

Study Objective:

This study is designed to determine if intravenously administered terbutaline will cause a change in the concentration of phospholipids known to be important in the surfactant system of adult lungs.

Technical Approach:

Two groups of 8 mixed sex adult beagle dogs each will be used in the study. One group will receive 250 ml of 0.9 percent NaCl intravenously over a 30-minute period; these will serve as controls. One-half of these animals will be sacrificed at one hour, and the other half at four hours. The other group will receive 250 ml of 0.9 percent NaCl containing 0.5 mg of terbutaline intravenously over a 30-minute period and will be similarly sacrificed. Portions of lung and alveolar washings from each animal will be freshly obtained and studied for content of total phospholipid, lecithin, sphingomyelin, phosphatidyl inositol and phosphatidyl glycerol. We will then compare the groups to determine any changes in the phospholipid content over the period of time that we investigated.

Progress:

This protocol was not activated until September 1982. The remaining animals will be entered early in FY83 and the samples analyzed throughout FY83.



# Detail Summary Sheet

Date: 1 Oct 82 Prot No: 81/61 Status: Completed

## Title:

Maternal and Fetal Effects of Verapamil, A Calcium Blocking Agent

Start Date:

Est Comp Date:

Principal Investigator:

Facility:

Daniel L. Vaughn, M.D.

Dept/Sec:

Assoc Investigators

Key Words:

Verapamil

Accumulative MEDCASE

Est

Periodic

Cost

OMA Cost: \$107(1337)

Review Results

Study Objective:

This project is designed as a preliminary study to evaluate the effect of Verapamil on cardiovascular functions in pregnant ewes and their fetuses. Based on these findings, further studies will be done on the use of Verapamil as a tocolytic agent in the prevention of premature labor.

## Technical Approach:

Ten near term pregnant ewes will be used. Spinal anesthesia will be administered using 8 mg xylocaine and light sedation obtained by giving 10 mg diazepam intramuscularly. Under separate local anesthesia, one carotid artery and jugular vein will be cannulated. The carotid catheter will serve to monitor maternal arterial pressure and heart rate and to collect arterial blood samples anaerobically. The jugular vein catheter will be used to monitor venous pressure and to administer Verapamil. The pregnant uterine horn will then be exposed through a midline incision and marsupialized to the abdominal wall to prevent excision. The fetus will then be delivered and marsupialized to the edges of the uterine incision to protect the umbilical circulation. The head will be covered with a saline filled glove to prevent respiration. An indwelling catheter will be placed into an umbilical vein through an intercotyledonary branch and serve for anaerobic collection of umbilical vein blood samples and for monitoring the umbilical vein pressure.

The fetal femoral artery and vein will be cannulated; the femoral artery catheter will serve for the collection of blood samples and for monitoring fetal arterial pressure and heart rate. The venous catheter will serve for replacing blood collected for blood gases.

with like volumes of maternal blood. Finally, an abdominal incision will be made in the fetus just above the cord attachment. Through this incision the umbilical vein will be exposed and a flow transducer attached. Local anesthesia will be used for the fetal surgery.

Following surgical preparation and stabilization of cardiovascular functions, a 30-minute control period, followed by a 2-hour experimental period of Verapamil administration, followed by a 30 minute recovery period will be conducted. Each animal will serve as its own control and the following parameters will be monitored:

- Maternal:
1. Arterial blood pressure
  2. Heart rate
  3. Venous blood pressure
  4. Arterial  $PO_2$ ,  $PCO_2$ , PH,  $O_2$  saturation, and base excess
  5. Umbilical vein  $PO_2$ ,  $PCO_2$ , PH,  $O_2$  saturation and base excess
  6. Umbilical vein flow

Verapamil will be administered intravenously at the rate of 0.1 mg/kg as a bolus dose, followed by 0.005 mg/kg/min in a continuous infusion. These doses are considered therapeutic in humans.

At the end of the experiment, the ewe and fetus will be sacrificed by the administration of a saturated solution of KCl intravenously.

It is felt that this experimental design will allow the detection of any significant derangement of cardiovascular or placental function resulting from Verapamil administration.

#### Progress:

Verapamil, a calcium blocking agent whose principal effect is relaxation of smooth muscle, was studied by measurement of cardiovascular parameters of seven near-term pregnant ewes and their fetuses during intravenous infusion of the drug. Verapamil caused a transient mild bradycardia and blood pressure drop in the ewe that rapidly returned to control levels 5-10 minutes after initiation of the infusion. No changes were noted in fetal arterial pressure, pulse, umbilical blood flow, or blood gases. Verapamil may be a useful drug in abating premature labor and these experiments indicate that no significant adverse effects on maternal or fetal cardiovascular function result from its use.

# Detail Summary Sheet

Date: 1 Oct 82      Prot No: 82/38      Status: Ongoing

Title:  
A Comparison of P.O. Vibramycin with IM Kefzol for Prophylaxis in Vaginal Hysterectomy

Start Date:      Est Comp Date:  
Principal Investigator:      Facility:  
CPT J.B. Stanley, MC

Dept/Sec: Dept Ob-Gyn      Assoc Investigators  
Key Words:  
Vibramycin; Kefzol; Vaginal hysterectomy

Accumulative MEDCARE      Est      Periodic  
Cost      OMA Cost:      Review Results  
Study Objective:

To compare the effectiveness of an inexpensive oral antibiotic to a more expensive and painful method of prophylaxis.

## Technical Approach:

Each patient to undergo vaginal hysterectomy at WBANC will be counselled as to the need for antibiotic prophylaxis and the usual routine for administration. The study will be explained to the patient and if not allergic to either drug, they will be asked to give written consent to join the study group. Upon entering the study group, the patient will receive two capsules at 2400 hours the night prior to surgery and an IM injection prior to going to the operating room. The study will be double blinded with all medications being distributed by the pharmacy after they have randomly selected which patients will be in each group. The two capsules taken by the patient will contain a total of 200 mg of vibramycin or a placebo. Those obtaining the vibramycin will receive an IM injection of normal saline diluted with Solu-B complex to match the color of the Kefzol solution, the next day on call from the operating room. The patient receiving the placebo capsules will receive 1 gm Kefzol IM on call from the operating room, prior to surgery. Oral vibramycin has been selected because no oral cephalosporin has ever been available and vibramycin fits all the criteria for an effective prophylactic antibiotic as set forth by Drs. Duff and Park.

The study will commence as soon as the protocol is approved and will end after 100 patients have been entered. To evaluate the study, the definition of febrile morbidity set forth by the Joint Committee on Maternal Welfare will be used: i.e., an oral temperature of 38C on two separate occasions, exclusive of the first 24 postoperative hours. Any patient developing postoperative complications would be treated with the appropriate methods, whether they are in the study group or not. Groups will be compared by  $X^2$  analysis.

#### PROGRESS

Patient entry is continuing. The code will be broken when the predesignated number of subjects have completed the study.

# Detail Summary Sheet

Date: 1 Oct 82 Prot No: 82/56 Status: Completed

## Title:

Acute Cardiovascular Effects of Delta-9-Tetrahydrocannabinol In Anesthetized Pregnant Sheep

Start Date:

Est Comp Date:

Principal Investigator:

Facility:

LTC R.W. Cotterill, MC

Dept/Sec: Dept Ob-Gyn

Assoc Investigators:

Key Words:

Delta-9-THC; Anesthetized pregnant sheep

Accumulative MEDCASE

Est

Periodic

Cost

OMA Cost: \$900(900) Review Results

Study Objective:

To delineate the acute effects of bolus injections of delta 9 THC on maternal and fetal cardiovascular parameters and acid base balance. Exhaustive bibliographies referencing scientific publications on marihuana indicate a paucity of information regarding the effects of marihuana, or marihuana constituents on physiological parameters during gestation. We have previously investigated the effects of bolus injections of 1 mg/kg and 2 mg/kg of delta 9 THC on uterine and placental perfusion utilizing a discrete measurement technique in the rabbit. Fourteen of fourteen animals so studied demonstrated decreased placental perfusion one hour following the dose of THC. Cardiac output determinations were not done in this experiment and we could not ascertain whether the effects noted were primary or secondary to systemic toxicity.

## Technical Approach:

Five pregnant sheep, unused in protocol 81/61 will be used for this study. Preparation of the animal has been previously described in Protocol 81/61. Following placement of the catheters and a period of baseline monitoring of both cardiovascular parameters and acid base values, delta-9-tetrahydrocannabinol in a dose of 1 mg/kg will be administered as a bolus injection into the pulmonary artery. Based on the response in this sheep, the other animals will be studied either at the same dose or at lower doses. Cardiac output will be determined at 3, 5, 15 and 60 minutes post-injection. The fetal and maternal heart rate and blood pressure will be continuously monitored. Blood gases will be drawn at 3, 15, 60, 120 and 180 minutes. Monitoring will be conducted for three hours in all animals, or until any noted effects return to baseline. At least four animals will be studied at the same dose, and these animals' mean baseline values will be compared with the monitored values for statistical purposes using a paired t-test. Following the experiment the sheep will be overdosed with pentobarbital and destroyed. Portions of the serum samples removed coincidentally with each blood gas study will be saved for possible assay of the THC.

#### Progress:

The effects of pulmonary artery infusion of delta-9-tetrahydrocannabinol, 0.5 mg/kg, have been studied in four pregnant sheep. Cardiac output (CO) decreased from a baseline of  $4.49 \pm 0.91$  l/min (mean  $\pm$  SEM) to  $4.19 \pm 0.87$  at 3 min,  $3.69 \pm 0.76$  at 5 min and  $3.35 \pm 0.77$  at 15 minutes post-infusion and returned to baseline by one hour post-infusion. Maternal blood pressure (MBP) decreased from  $114 \pm 9$  to a nadir of  $69 \pm 8$  mm/Hg at 15 minutes post-infusion. Uterine artery blood flow (UTABF) increased from  $256 \pm 88$  to  $317 \pm 132$  ml/min at 3 minutes post-infusion, but this was not statistically significant. Maternal acidosis, hypercapnia and hypoxemia also developed during the first 15 minutes post-infusion. Although fetal blood pressure (FBP) decreased throughout the first hour post-infusion, statistically significant changes in FBP or fetal heart rate (FHR) were not observed. Umbilical artery blood flow (UMABF) increased from  $188 \pm 58$  to  $211 \pm 68$  l/min at five minutes post-infusion and declined thereafter. These changes were also not statistically significant. As in the ewe the fetus developed acidosis and hypoxemia, but hypercapnia, although present, was not statistically significant. A single animal was studied following intravenous infusion of delta-9-tetrahydrocannabinol, 1 mg/kg. Similar, but more pronounced, effects were noted. The sheep were maintained under pentobarbital anesthesia for the duration of the study.

# Detail Summary Sheet

Date: 1 Oct 82 Prot No: 92/58 Status: Ongoing

## Title:

A Longitudinal Study of T Cells In Pregnancy

Start Date:

Est Comp Date:

Principal Investigator:

Facility:

CPT Steven Gardner, MC

Dept/Sec: Dept Ob-Gyn

Assoc Investigators

Key Words:

T-cells; pregnancy

Accumulative MEDCASE

Est

Periodic

Cost

OMA Cost

Review Results

Study Objective:

To determine in a longitudinal manner concentrations of helper/inducer, suppressor/cytotoxic and all peripheral t-cells during normal pregnancy.

## Technical Approach:

Fifteen to twenty volunteers will be selected from the Family Planning Clinic at the time they discontinued contraceptive measures. If an IUD or oral contraceptive was in use, baseline samples, and repeat samples at three and six week intervals, will be drawn to ascertain the stability of the controls. Those who conceive will be sampled at 6, 12, 18, 24, 30 and 36 weeks of pregnancy and again 6, 12, and 18 weeks postpartum. A single sample will be obtained during the first stage of labor. Twenty ml of heparinized blood will be removed each time so the total during pregnancy will be 140 ml. The t-cell subsets will be counted using the technique described in Reference 1, with minor modifications or utilizing fluorescent activated cell sorting should that equipment be functional in our laboratory by the time the experiment is underway. Paired t test will be used to determine significance. If possible, a cohort of nonpregnant women will be studied in a parallel manner.

## Progress:

Patient entry has not commenced on this newly approved protocol.

Detail Summary Sheet

Date: 1 Oct 82 Prot No: 76/24 Status: Terminated

Title:

An Investigation of the Effects of Supplemental Oxygen on Chemically Induced Fat Embolization

Start Date:

Est Comp Date:

Principal Investigator:

Facility:

COL D.A. Vichick, MC

Dept/Sec: Orthopedics

Assoc Investigators

Key Words:

Embolization; Oleic acid

Accumulative MEDCASE  
Cost

Est  
OMA Cost:

Periodic  
Review Results

Study Objective:

To determine whether or not supplemental oxygen prevents or lessens the potentially lethal effects of chemically induced fat embolization in dogs.

Technical Approach:

Clinical observations, as well as lung scans, are generally accepted as criteria for determination of the presence of fat embolism syndrome. In this study laboratory parameters and lung scans are obtained for five-day periods in beagles following injection of oleic acid. This data is collected from dogs supported on either room air or supplemental oxygen.

Progress:

None.



# Detail Summary Sheet

Date: 1 Oct 82 Prot No: 70/01 Status: Completed

Title:  
Compartmental Pressure Studies as a Determinant for the Need for  
Fasciotomy

Start Date: Est. Comp. Date:  
Principal Investigator: Facility:

COL D.A. Vichick, MC

Dept/Sec: Orthopedics Name: Investigator  
Key Words:

Fasciotomy

Accumulative MEDICASE Est Periodic  
Cost \$5,430 OMA Cost: Review Results  
Study Objective:

Trauma (insult) to muscles will be followed by an injury reaction resulting in swelling (interstitial)(intercellular) of the involved muscle or muscles. If the traumatized muscles are contained within a nonyielding compartment, increased intracompartmental pressure can reach a level where it exceeds perfusion pressure (diastolic or venous pressure) although distal pulses may be present. As the pressure within the compartment approaches the systolic pressure of the patient there is no tissue perfusion and the distal pulses are absent. Studies in dogs have shown that the tissue injury increases as the duration of the ischemia increases. The impedance of capillary flow and venous drainage will get a stage for increased swelling followed by increased venous blockage until the intracompartmental pressure can exceed the arterial pressure in the small vessels of the involved muscles. The state of ischemia caused by the increase in intracompartmental pressure can lead to necrosis and death of the involved muscles.

Clinical experience has demonstrated the ability to prevent muscle necrosis as a result of increased compartmental/intracompartmental pressure by performing a fasciotomy thus converting the closed and nonyielding space to an expandable area. The clinical parameters of compartment syndrome are: (a) Increased circumference of the extremity. (b) Increased pain of the involved area out of proportion to the injury and accentuated by voluntary motor effort. (c) Decreased motor power of the involved muscle group. (d) Decreased distal sensation. (e) Decreased quality of distal pulses.

The clinical criteria for a fasciotomy do not possess a high degree of sensitivity in indicating the necessity for fasciotomy. Thus errors of omission (delaying fasciotomy too long) and commission (performing fasciotomy when it is truly not needed) are still more frequent than desirable. It has been determined by Whitesides, et al., that as tissue pressure readings equal or exceed 30 millimeters of mercury, the patient must be carefully followed with periodic tissue pressure readings and monitoring of all signs and symptoms of a closed compartment syndrome. Further, as tissue pressures approach or equal the patient's diastolic pressure, a fasciotomy is definitely indicated. Tissue pressures of 40-45 mm of mercury should usually be the upper limit prior to fasciotomy when the diastolic pressure is in the range of 70mm of mercury. It was found that tissue recovery is essentially complete after four hours of ischemia, but only 50 percent complete after six hours of ischemia. The damage is extensive and irreversible after eight hours of ischemia. The contained neurotissues are even more sensitive to ischemia than muscle and thus the duration of ischemia is even more critical following prolonged increase of intracompartmental pressures.

A study will be conducted in which intracompartmental pressures of the anterior and posterior compartments of the legs, anterior and posterior compartments of the forearm, and dorsal interosseous compartments of the hand will be measured in various states of normal, stress and following disease or injury. The intracompartmental pressure values will be correlated with the clinical picture (pain, increased circumference, decreased motor activity and/or sensation, and quality of distal pulses). When possible and feasible, the uninjured extremity will be used as a control. During this study, fasciotomy will be performed using the accepted clinical indications without regard to the values as determined by the intracompartmental pressure studies alone.

Three categories of patients will be tested, each group consisting of 25 but not more than 50 patients. The categories will be as follows:

Group 1: Normal volunteers (or noninvolved extremities of Group 3 patients).

Group 2: Volunteers who will perform strenuous physical activity with the involved extremity while compartmental pressures are monitored: before, during and after activity.

Group 3: Volunteer patients who by way of disease or injury are suspected of having increased compartmental pressures of the lower leg, forearm, or dorsum of the hand.

A 22 or 24-gauge intracath will be inserted into the compartment to be studied or in question, both in the lower and upper extremity following a sterile prep of the area. The site selected for insertion will be determined by the investigator. The areas where muscle is felt to be compromised or to be normal will be studied primarily. Areas that closely surround fractures or known hematomas will be avoided if possible. The exact technique for recording intracompartmental pressures will be same as described by Matsen et al. During the study the compartment pressures will be obtained and correlated with the clinical picture, a determination will be made as to whether intracompartment pressures offer a significant advantage in determining the need for fasciotomy over known clinical parameters. The risk of the study to the volunteer participants is considered to be minimal and no greater than would occur with any intramuscular injection with a small bore needle.

#### Progress:

An abstract of the data collected during the past three years was presented at the Annual Meeting of the Western Orthopaedic Association, 11-15 Oct 1982.

# Detail Summary Sheet

Date: 1 Oct 82 Prot No: 79/42 Status: Completed

## Title:

The Incidence of Visual-Motor Perceptual Problems in Persons with Traumatic Hand Injuries

Start Date:

Est Comp Date:

Principal Investigator:

Facility:

MAJ M.J. Baker, AMSC

Dept/Sec: Orthopedics

Assoc Investigators

Key Words:

Trauma, Hand

Accumulative MEDCASE

Est

Periodic

Cost

OMA Cost:

Review Results

Study Objective:

To determine if persons with traumatic hand injuries have pre-existing visual motor perceptual problems which may have led to their trauma.

Technical Approach:

It is recognized by the Federal Government, school systems, and medical professionals that children may suffer from minimal brain dysfunction and/or developmental disabilities resulting in sensory-motor integration problems or inability to perform classroom and play activities in a manner appropriate for their age. In interviews of individuals with traumatic hand injuries it appears that these individuals may not know where their hands are in space and, therefore, suffer from a visual-motor perceptual problem, a form of sensory-motor integration.

The Slosson Drawing Coordination Test is reported to "screen out individuals suffering from serious forms of brain dysfunction or damage where eye-hand coordination is involved." "A reliability coefficient of .96 was obtained for a group of 200 individuals, aged 4 to 52 years." This test does not screen out individuals with emotional problems due to brain dysfunction nor does it identify individuals with eye-hand incoordination due to a specific visual-motor perceptual problem. The Kinesthesia Test of the Southern California Sensory Integration Test is intended to measure the capacity to perceive joint position and movement. Although this test is standardized for individuals from 4 to 8 years of age, it is felt to be an indicator of individuals unable to perceive their extremities in space, that is, visual-motor perceptual dysfunction.

a. The specific purpose of this study is to determine if individuals with traumatic hand injuries also have a pre-existing visual-motor perceptual problem as measured by the Slosson Drawing Coordination Test and the Kinesthesia Test of the Southern California Sensory Integration Tests.

b. The number of subjects for the study will be 20 persons with traumatic hand injuries. The age range of these individuals will be 18 to 30 years of age; they will be active duty military, males and females.

#### Progress:

In this study 100 active duty military persons, ages 18 to 30, were tested for visual motor perceptual problems using the Slosson Drawing Coordination Test and the Ayres Kinesthesia Test. Fifty of these persons had traumatic hand injuries, that is injuries that were self-inflicted and traumatic in nature. The remaining fifty were basic trainees and volunteers who considered themselves healthy. Both groups filled out a brief history of past injuries. Both groups did equally well on the Ayres Kinesthesia Test. While the Slosson Drawing Coordination Test was not significant in discriminating persons with visual motor perceptual problems, it may have been significant in identifying individuals with sensory emotional problems. These individuals were also persons who had self-inflicted traumatic hand injuries.

# Detail Summary Sheet

Date: 1 Oct 82 Prot No: 82/60 Status: Ongoing

## Title:

Interactions Between Aminoglycoside Antibiotics and Vitamin B6 in vitro and in vivo

Start Date:

Est Comp Date:

Principal Investigator:

Facility:

MAJ R.C. Keniston, MC

Dept/Sec: Dept Pathology

Assoc Investigators

Key Words:

Aminoglycosides; Vitamin B6

Accumulative MEDCASE

Est

Periodic

Cost

OMA Cost:

Review Results

Study Objective:

To develop a method for isolating and quantitating aminoglycosidepyridoxal 5'-phosphate complexes. To isolate these complexes from the urine of patients receiving the aminoglycoside antibiotics. To determine if depletion of vitamin B6 occurs in patients receiving aminoglycoside antibiotics, and if so, how this depletion correlates with morbidity and mortality.

Technical Approach:

Subjects will be patients who are to be given aminoglycoside antibiotics for clinical indications (sepsis, serious gram-negative infections, etc). These patients should also have SHAC 20 chemistry screens and monitoring of their aminoglycoside levels (procedures already routinely performed). The blood and urine samples from at least 30 patients will be examined.

Progress:

Patient entry has not begun on this newly approved protocol.

Detail Summary Sheet

Date: 1 Oct 82 Prot No: 77/10 Status: Completed

Title:

Zinc Levels in Maternal Infant Pairs

Start Date:

Est Comp Date:

Principal Investigator:

Facility:

COL L.L. Penney, MC

Dept/Sec:

Assoc Investigators

Key Words:

Zinc; Trace elements

Accumulative MEDCASE

Est

Periodic

Cost

ONA Cost: \$800(4479

Review Budget

Study Objective:

To determine the zinc level in maternal infant pairs and to see if there is a correlation with the incidence of infection.

Technical Approach:

Zinc and phosphate concentrations in maternal and neonatal cord blood will be correlated with the incidence of neonatal sepsis in a blind retrospective study. The hypothesis of increasing zinc and phosphate levels in enhanced amniotic fluid bactericidal activity will be studied.

Progress:

Maternal venous blood and infant cord blood were obtained at time of delivery. Blood was drawn with disposable plastic syringes and stainless steel needles. Blood was delivered and centrifuged in plastic tubes. Serum was removed and stored at 4C until analyzed. All materials used for collection, handling, and storage were examined for zinc contamination. Precautionary measures were taken to avoid contamination during analysis.

All zinc determinations were made on an Instrumentation Laboratory Model 751 Atomic Adsorption Spectrophotometer using a single stat burner head. An acetylene flame was utilized with a fuel air mixture giving a lean blue flame. Wavelength was set at 213.9nm, lamp current 3mA, slit width 320 nm, burner height 8mm, and aspiration rate of 5 ml/min. Readings were taken at 1 sec intervals for a total of ten readings and averaged.

Copy available to DDC by request  
permit fully 1/2/83

Deionized distilled water made 0.016 M HCl was used for all dilutions and standards. Serum was diluted 1:10 using a Labindustries Repipetor and aspirated directly into the mixing chamber.

Analyses of biological fluids for trace metals are subject to analytical error primarily due to the ease of sample contamination. Literature values for serum zinc levels vary from 84 ug/dl to 428 ug/dl in normal human subjects. It is important, therefore, to establish a norm for a given population of subjects and for a given analytical laboratory.

The importance attached to maintenance of adequate zinc levels during pregnancy led us to collect data on a limited number of pregnancies during the first trimester and an extensive number of mothers at delivery and infant cord blood samples. Reported zinc levels during pregnancy vary, but there is general agreement that serum zinc levels decrease during pregnancy while infant cord bloods tend to be higher than the mother's serum level at delivery (Table I). This is consistent with the importance of zinc in fetal development in that the fetus is capable of actively concentrating zinc at the mother's expense.

The values reported here are from patients delivering at William Beaumont Army Medical Center in El Paso, Texas. However, due to the highly mobile nature of the military population, these values are not necessarily representative of the local population.

The mean serum zinc value for 53 women during the first trimester of pregnancy was found to be  $98 \text{ ug/dl} \pm 2.7$  (s.e.m.). This value corresponds well with most literature values for normal serum zinc levels for females. The distribution of the values from this small sample of patients was rather broad (range 45-150 ug/dl, and skewed to lower values. This was due to the small size of the sample and the differences in the time into the pregnancy.

The mean serum zinc value for 411 women at delivery was  $66 \pm 1.3$  (s.e.m.) ug/dl representing a 33% decrease in mean maternal zinc levels for the course of the pregnancy. Values were very nearly normally distributed about the mean, but slightly skewed to higher values.

The cord blood mean serum zinc level from 758 infants was found to be  $79 \pm 0.9$  (s.e.m.) ug/dl. The fetus therefore must be capable of concentrating zinc at the expense of the mother. The distribution of values about the mean for this large sample was almost normally distributed.



The values reported here agree well with published values both in the absolute zinc concentrations as well as in the changes in zinc during the course of pregnancy.

Copper is also an important trace element with a variation in serum levels during pregnancy. Serum copper levels were determined for a smaller group of mothers and infants during this study. Mean copper levels were found to increase from the first trimester (18 ug/dl to 231 ug/dl) at delivery. The cord blood value of 62 ug/dl was severely depressed relative to that of the maternal serum. The increase in the copper-zinc ratio indicates an inverse relationship between the two trace metals.

Efforts will be made to determine if correlations can be made between zinc deficiency and neonatal well being. Continued results will be included and reported with protocol 81/03

# Detail Summary Sheet

Date: 1 Oct 82 Prot No: 77/13 Status: Terminated

Title:

Investigation of the Effects of Diphenylhydantoin on Intellectual Functioning of Children

Start Date:

Est Comp Date:

Principal Investigator:

Facility:

LTC P.F. LoPiccolo, MC

Dept/Sec: Pediatrics

Assoc Investigators

Key Words:

Diphenylhydantoin

Accumulative MEDCASE

Est

Periodic

Cost

OMA Cost:

Review Results

Study Objective:

To determine if Dilantin has any effect on intellectual functioning.

Technical Approach:

To test children over the age of six years who have been placed on phenobarbital or dilantin because of a new seizure disorder. To test children who have been on long term anticonvulsants to see if there has been any change in intellectual function. This can only be accomplished if children had educational and psychological evaluations before the onset of their seizure disorder. Testing is being accomplished by Psychology using the WISC-R. The first part of the study has gone slowly because we have had very few cases of new spontaneous seizure disorders in children over the age of six years.

Progress:

Insufficient numbers of patients have been available for study.

Detail Summary Sheet

Date: 1 Oct 82 Prot No: 78/25 Status: Completed  
Title:

Antibiotic Prophylaxis for Recurrent Otitis Media: Comparison of  
Sulfasoxizole, Erythromycin, and Placebo

Start Date: Est Comp Date:  
Principal Investigator: Facility:

LTC M. Weir, MC

Dept/Sec: Pediatrics Assoc Investigators  
Key Words:

Otitis media

Accumulative MEDCASE Est Periodic  
Cost QMA Cost: Review Results  
Study Objective:

To compare the effect of chronic administration of oral  
sulfasoxizole, erythromycin or placebo upon the number of ear  
infections in children with a history of recurrent otitis media

Technical Approach:

Children under the age of six years who, upon review of their  
outpatient chart, have a documented history of four or more ear  
infections in the preceding twelve months will be considered  
eligible for the study. Children with previous history of PE tubes,  
cleft palate or immune disease will be excluded. After informed  
parental consent, the children will be placed on either  
sulfasoxizole 25 mgm/kg/dose b.i.d., erythromycin 10 mgm/kg/dose  
b.i.d., or placebo for a three-month period. During this time the  
patient will be followed monthly with impedance tympanometry and  
physical examination. Any new ear infections during this period  
will be treated with systemic antibiotics for ten days. During the  
second and third three-month period an alternate drug will be used.  
Each patient will be followed for nine months and will serve as his,  
or her, own control. (Three months on Sulfasoxizole, 3 months on  
placebo, 3 months on erythromycin) in random order. At the  
conclusion of the study, the frequency of ear infections in children  
receiving placebo will be compared to those receiving sulfasoxizole  
or erythromycin.

## Progress:

Recurrent otitis media among infants and children is a common management problem. Antibiotic prophylaxis with ampicillin, sulfasoxazole or trimethoprim/sulfamethoxazole reduces the frequency of otitis media in children when compared to placebo. We evaluated erythromycin as prophylaxis for recurrent otitis media, since it has in vitro activity against common middle ear pathogens; and its use avoids both the side effects associated with sulfonamides and the risk of ampicillin resistance in oral flora. Children with a documented history of four or more discrete episodes of otitis media in the preceding year or three discrete episodes in the preceding six months, were given erythromycin ethylsuccinate 10 mgm/kg/dose, b.i.d., for two months, followed by two months observation. Forty-five children were enrolled and followed with pneumatic otoscopy and tympanometry during a 12-month period. Eight of 45 children (18%) developed otitis media while receiving erythromycin prophylaxis. Twenty-two of 41 children (54%) developed otitis media while receiving no prophylaxis ( $p$  less than 0.01). Five of the eight children who developed otitis media while receiving erythromycin had middle ear fluid cultures (four by tympanocentesis and one spontaneous perforation); three were Staphylococcus epidermidis and two were Haemophilus influenzae. The attack rate (number of acute otitis media episodes per child per two month period) was 0.87 for children prior to entry into the study, 0.20 for children receiving erythromycin prophylaxis and 0.81 for children when the erythromycin prophylaxis was stopped ( $p$  0.01). No untoward or unusual reactions occurred while receiving erythromycin prophylaxis. We conclude that erythromycin ethylsuccinate is safe, effective antibiotic prophylaxis for children with recurrent otitis media.

# Detail Summary Sheet

Date: 1 Oct 82 Prot No: 80/2 Status: Ongoing

## Title:

Developmental Analysis of Heavy and Trace Element Hair Content in Normal Children and Children with Attention Disorders

Start Date:

Est Comp Date:

Principal Investigator:

Facility:

COL P. LoPiccolo, MC

Dept/Sec: Pediatrics

Assoc Investigators

Key Words:

Trace elements

Accumulative MEDCASE

Est

Periodic

Cost

OMA Cost: \$605 (605)

Review Results

Study Objective:

To investigate developmental changes in the influence of heavy and trace elements on the behavior of normal children and children with attention disorders.

Technical Approach:

Twenty-five normal children and twenty-five children who have been diagnosed as having an attention disorder with excessive activity will be selected from each of the following age groups: Seven-year olds, nine-year-olds, and eleven-year-olds. An additional group of nine-year-old attentional-disordered children will be selected who are currently on medication. One tablespoon of hair will be collected from the nape of the neck. Ten mm of hair nearest the skin will be trimmed to provide the sample. Information will also be solicited regarding such areas as the date of the most recent hair washing, use of medication, and diagnostic status. Achievement information for the normal children will be acquired using the Wide Range Achievement Test (WRAT), while intelligence scores will be computed using the Peabody Picture Vocabulary Test (PPVT). The hair samples will be stored in plastic bags and coded in a manner so that an individual child's name is not associated with the results. Once the required number of hair samples has been acquired, the samples will be analyzed using atomic absorption spectroscopy. Comparisons of each of the element levels for the normal and attention disordered children will be made in order to identify a possible relationship between the levels of certain elements and the performance of certain intellectual activities.

**Progress:**

Specimen collection is complete. Analysis has been slowed by malfunctions of the AA spectrometer and electrical mechanical modifications of the facility. The sera has been run twice with inconsistent results. The complete set will be analyzed again and correlations sought. The data reduction will be done by the associate investigator as the principal investigator has been reassigned.

# Detail Summary Sheet

Date: 1 Oct 82 Prot No: 80/34 Status: Completed

Title:

Counterimmunoelectrophoresis In Nonsuppurative Otitis Media

Start Date:

Est Comp Date:

Principal Investigator:

Facility:

LTC M. Weir, MC

Dept/Sec: Pediatrics

Assoc Investigators:

Key Words:

Otitis media; Counterimmunoelectrophoresis

Accumulative MEDCASE

Est

Periodic

Cost

OMA Cost: \$802(1002)

Review Results

Study Objective:

Test the possibility that antigen persists in middle ear fluid after suppurative becomes nonsuppurative otitis media. It is known that 20-30 percent of middle ear effusions will remain culture positive after the standard course of ten days of antibiotics and even though the fluid on followup examinations has become serous. Further evidence of persistent infection would alter therapy in that initiation or continuation of antibiotics might be indicated. That is, patients who present with serous fluid or develop serous fluid after a standard ten day course of antibiotics may need antibiotic therapy. Twenty to thirty patients will be screened in this pilot study and if persistent infection appears common, a study of extended treatment regimens will be proposed.

Technical Approach:

The usual indications for myringotomy and PE tubes include persistent or recurrent suppurative and nonsuppurative otitis media. The duration criterion for persistence of nonsuppurative otitis media is 2-3 months. This, with or without a conductive hearing loss, is the most common indication for the procedure. Patients are normally referred from Pediatrics to ENT for consideration for the procedure. Patient selection will be by the ENT specialist and not by the primary investigator. When the procedure is performed, the middle ear effusions will be aspirated, the aspirate preserved in a mucus trap, and transported to the laboratory for CIE, culture and gram stain. Aspiration is standard and no additional risk will result from this study.

Progress:

Fifteen patients were enrolled. No positives were found. No additional patients will be studied.

# Detail Summary Sheet

Date: 1 Oct 82 Prot No: 81/42 Status: Ongoing

## Title:

The Recognition and Frequency of the Polycystic Ovary Syndrome in a General Adolescent Population

Start Date:

Est Comp Date:

Principal Investigator:

Facility:

CPT W.R. LaForce, MC

Dept/Sec: Pediatrics

Assoc Investigators

Key Words:

Polycystic ovary syndrome

Accumulative MEDCASE

Est

Periodic

Cost

OMA Cost: \$0(2852)

Review Results

Study Objective:

To establish the frequency of biochemically proven polycystic ovary syndrome (PCOS) in a general adolescent clinic population, and to evaluate parameters of the medical history in its early recognition.

## Technical Approach:

Each year in May through August days are set aside for school and sports physical examinations for dependent children at WBAMC. Approximately 350 adolescent girls are examined on these days. Sera will be collected from approximately 200 of these adolescents after patient and parental consent, and a menstrual history will be obtained. Serologic RIA tests will include the gonadotropins LH and FSH, and the androgen testosterone. Aliquots of serum will be kept frozen for possible subsequent hormone analysis to include estrone, estradiol, androstenedione and insulin. Elevated levels of testosterone, and/or elevated LH, with associated low values of FSH, are biochemical evidence of the polycystic ovary syndrome. Patients characterized as cases of this syndrome will be asked to return to the Adolescent Medicine Clinic for further evaluation, including more comprehensive medical history, and pelvic examination. Those cases identified will be counselled regarding future fertility problems, and offered biochemical regulation of their menstrual periods in an effort to offset the symptoms of this disorder.

## Progress:

No additional samples have been drawn. The specimens are being analyzed for progesterone to determine the phase of the cycle and the data will be reorganized accordingly for analysis.



Detail Summary Sheet

Date: 1 Oct 82      Prot No: 81/59      Status: Terminated  
Title: A Longitudinal Prospective Study of the Neurological and  
Electrophysiologic Development of the Postmature Child

Start Date:      Est Comp Date:      Facility:  
Principal Investigator:

MAJ Ernest F. Krug, MC

Dept/Sec: Pediatrics      Assoc Investigators  
Key Words:

Postmaturity

Accumulative MEDCASE      Est      Periodic  
Cost      OMA Cost:      Review Results  
Study Objective:

It is currently held that postmaturity may be associated with developmental delays. A recent study of children with developmental delay in language acquisition and electroencephalographic abnormalities in the absence of a seizure disorder has revealed that five out of seven children were postmature. To the best of our knowledge, no serial developmental and electroencephalographic studies have been conducted on postmature children without other pathological conditions up to the present. The purpose of this study would be to fill that gap.

Technical Approach:

A subgroup of postmature children would be identified and included in the study according to standard criteria for postmaturity. The remainder of this group would be infants born at a comparable period postdates but without the usually accepted stigmata of "postmaturity syndrome." These infants would all be compared to a group of normal infants born on or near their due date. Parents would be contacted for informed consent. All participants, control and study, will give the same informed consent. The patient would be studied in a planned longitudinal fashion as follows:

The Brazelton Neonatal Assessment Scale (Brazelton, 1973) would be administered on the 2nd and between the 28th and 30th day of life. A portable EEG would be performed in the Nursery prior to discharge from the hospital and a repeat study carried out at the age of three months and at the age of eighteen months. A neurological exam would

be performed at one year and 18 months. A speech evaluation would be performed at two years and optimally at three years of age. This would be carried out either through a standard evaluation or through a followup questionnaire.

**Progress:**

This project was terminated after five months because of insufficient numbers of patients due partially to reluctance of parents to sign the consent form.

# Detail Summary Sheet

Date: 1 Oct 82      Prot No: 81/62      Status: Completed  
 Title: Treatment of Middle Ear Effusions with Oral Hydrocortisone Versus Placebo

Start Date:      Est Comp Date:  
 Principal Investigator:      Facility:

LTC R.M. Lampe, MC

Dept/Sec:      Pediatrics      Assoc Investigators

Key Words:

Middle ear effusion; hydrocortisone

LTC H.R. Weir, MC

Accumulative MEDCASE      Est      Periodic  
 Cost      OMA Cost:      Review Results

Study Objective:

To determine the efficacy of oral hydrocortisone in the treatment of persistent middle ear effusion in infants and children.

## Technical Approach:

Infants and children (six months to 13 years) with persistent middle ear effusion (more than eight weeks) as determined by pneumatic otoscopy and tympanometry, despite systemic antibiotics, and decongestant/antihistamines will be eligible for the study. After informed parental consent, children will be randomly placed (blinded by the Pharmacy Service) on either oral hydrocortisone cypionate 6 mgm/kg/day in three divided doses for the first three days; 4 mgm/kg/day in two divided doses for the next two days; and one dose of 2 mgm/kg/day for one day or placebo (methyl cellulose prepared by the Pharmacy Service) with similar instructions for six days.

Audiometry and tympanometry will be performed prior to treatment and repeated at the one week and two week followup. After two weeks patients who are not cured (normal to improving pneumatic otoscopy and impedance tympanometry) will receive the crossover drug (placebo if hydrocortisone given initially; or hydrocortisone if placebo given initially) and will be followed weekly for two weeks.

Patients with persistent middle ear effusions for three months will be referred for myringotomy and PE tube placement. Patients who are cured will be followed at monthly intervals for six months with pneumatic otoscopy and impedance tympanometry.

The number of patients cleared or failed after initial therapy, crossover, and combined will be compared using chi-square.

Progress:

Thirteen patients with middle ear effusions were treated with steroids. Temporary improvement was noted in only three of eight patients, after one week of steroid treatment; and ventilating tubes were eventually placed in six of these eight patients. In this preliminary study, no benefit from steroid therapy for middle ear effusion was seen and no further patients will be enrolled. No untoward reactions or unusual infections were noted among these patients.

Detail Summary Sheet

Date: 1 Oct 82 Prot No: 81/66 Status: Ongoing  
Title: Single Day Therapy with Trimethoprim-Sulfamonomoxate for  
Lower Urinary Tract Infection

Start Date: Est Comp Date:  
Principal Investigator: Facility:

LTC R. Lampe, MC

Dept/Sec: Pediatrics Assoc Investigators  
Key Words:

Urinary tract infection

Accumulative MEDGASE Est Periodic  
Cost OMA Cost: Review Results  
Study Objective:

To determine if a single day of therapy is just as effective as ten days of therapy for lower urinary tract infection. Single day therapy would cut cost, potential development of resistant organisms would be reduced, and patient compliance would be increased.

Technical Approach:

Fifty children, ages 2-12 years will be studied. Children who would not be included: (1) Antibiotic therapy within previous 48 hours. (2) Diabetics. (3) Known anatomic or vascular abnormality of the kidney, or impaired renal function. (4) Any indication of upper urinary tract infection, i.e. flank pain, vomiting, fever greater than 38°C. (5) Known allergy to sulfa drugs.

The diagnosis of lower urinary tract infection will be based upon a) lower abdominal pain, b) frequency of urination, c) urgency or urination, d) dysuria, e) no fever, or fever less than 38°C, f) no flank pain or tenderness, g) child does not appear ill (toxic).

Laboratory: One or more of the following: a) unspun urine with bacteria but no casts. b) dipstick-nitrite positive. c) greater than 100,000 colonies on two clean catch urines. d) greater than 10,000-50,000 colonies on a catheterized specimen. e) any growth on a suprapubic aspiration of the bladder.

A complete blood count, ESR, and C-reactive protein will be drawn on all subjects in the study. Selection for single day vs. ten day therapy will be random. Fifty envelopes, twenty-five of which will contain the single day protocol, and twenty-five of which will contain the ten-day protocol, will be utilized for the selection.

The subjects of the study will receive 8 mg per kilogram body weight per dose of trimethoprim-sulfamethoxazole. They will receive one dose at the time they are seen in the clinic and one dose at bedtime that same day. The controls will receive 4 mg per kilogram body weight per dose of trimethoprim-sulfamethoxazole every twelve hours for a period of ten days.

Each child included in the study will be seen 48 hours after institution of therapy at which time a repeat urine microscopic, dipstick, and culture will be done. At that time children who will be excluded are: (1) initial negative urine culture (2) organism not sensitive to trimethoprim-sulfamethoxazole. (3) Any child who shows signs or symptoms of upper urinary tract infection.

Subsequent to the initial 48 hour followup each patient will be seen two weeks after initiation of therapy, then monthly for six months. All male children will also be studied for urinary tract abnormalities with an intravenous pyelogram and a voiding cystourethrogram.

#### Progress:

Thirteen patients have met the criteria for entry and have completed followup. Each of the nine patients receiving ten days of TMP-SMX, had sterile urine 48 hours after initiation of therapy and eight of nine patients had sterile urine two weeks after conclusion of therapy. Each of four patients receiving TMP-SMX for one day had sterile urine 48 hours after initiation of therapy; however, three of four patients had significant bacteriuria two weeks after conclusion of therapy. Seven patients had erythrocyte sedimentation rates obtained and all were less than 20mm per hour. Four of eight patients had positive C-reactive protein in the serum. Three of these four had bacteriuria two weeks after the conclusion of therapy (two were in the single day therapy group and one was in the ten day therapy group).

These preliminary results suggest that single day treatment may not be as satisfactory as 10 days TMP-SMX for urinary tract infection.

Detail Summary Sheet

Date: 1 Oct 82 Prot No: 82/09 Status: Ongoing

Title:

An Evaluation of the Effects of Theophylline and Beta Adrenergic Medication on the Auditory Processing Ability of Children

Start Date:

Est Comp Date:

Principal Investigator:  
CPT G.V. Gwinn, MC

Facility:

Dept/Sec: Dept Pediatrics

Assoc Investigators

Key Words:

Theophylline; B-adrenergic agents; Auditory processing

Accumulative MEDCASE  
Cost

Est  
OMA Cost:

Periodic  
Review Results

Study Objective:

To determine if the use of theophylline or beta adrenergic medications qualitatively or quantitatively affect the auditory processing abilities of children.

Technical Approach:

Twenty asthmatic children currently requiring continuous therapy with theophylline will be entered into the study. Serum theophylline levels will be checked to ensure that they are in the generally accepted therapeutic range of 10-20 micrograms per milliliter.

Each child will be evaluated using the Revised Token Test administered by personnel from the University of Texas at El Paso Speech, Hearing and Language Center. The reliability in the administration of this test is verified to be greater than 98%. The testers will be unaware of which medical regimen the children are on during any of the testing encounters.

Patients will then have their theophylline therapy discontinued and be placed on an inhaled beta-2 agent (Albuterol 180 micrograms) four times daily. Clinical experience suggests that most patients do equally well on this regimen. After one week on this new regimen, the testing will be repeated.

Patients whose clinical condition suggests that their asthma would be adequately controlled on inhaled beta-2 medication taken on an as needed basis will be placed on Albuterol every four to six hours as needed. After one week, they will be retested.

During the fourth week, the subjects will have the inhaled bronchodilators discontinued and once again be placed on their

theophylline regimen. After one week they will be tested once again.

The patient's pulmonary condition will be monitored by a diary sheet and twice daily Peak Expiratory Flow Rates. Conventional spirometry and flow volume determinations will be determined weekly.

After the results are analyzed each child will be placed on the regimen which gave best control of asthma and the least CNS effects.

The theophylline preparations used in this study will be whichever preparation the patient is taking on initiation of the study.

Statistical analysis will be done with nonparametric and parametric testing as deemed proper by our statistical consultant.

**Progress:**

Seven patients have been entered into the study. At least three more need to be entered. Dr. Gold has been transferred to Brooke Army Medical Center and Dr. Gwinn is the new principal investigator.



Detail Summary Sheet

Date: 1 Oct 82 Prot No: 82/28 Status: Ongoing

Title:

Sleep Patterns of Children and Adolescents

Start Date:

Est Comp Date:

Principal Investigator:

Facility:

COL P.F. LocPiccolo, MC

Dept/Sec: Dept Pediatrics

Assoc Investigators

Key Words:

Sleep patterns

Accumulative MEDCASE

Est

Periodic

Cost

OMA Cost:

Review Results

Study Objective:

To determine what are the normal behavior and ritualistic patterns of children/adolescents in regards to sleep. To determine if sleep patterns are predictive of any particular disorder of childhood ex: attentional deficit disorder. To determine what are normal parental behaviors in regards to sleep. To determine the incidence of sleep-walking, night terrors, enuresis and nightmares. To analyze school performance and its possible relationship to sleep patterns.

Technical Approach:

Parents who present to the Pediatric and Child Development Clinic will be asked if they would like to participate in this study. If so, a sleep and behavior questionnaire with a school behavior form will be given to them for completion. Analysis of the data obtained will be statistically analyzed by the Psychology Department at UTEP under the direction of Dr. Terry Allen.

Progress:

The data is being analyzed under the direction of the associate investigator. The principal investigator has been reassigned.

# Detail Summary Sheet

Date: 1 Oct 82 Prot No: 82/31 Status: Completed

Title:

Incidence of Rotavirus in Acute Diarrhea at WBAMC

Start Date:

Est Comp Date:

Principal Investigator:

Facility:

CPT G. Pereira, MC

Dept/Sec: Dept Pediatrics

Assoc Investigators

Key Words:

Rotavirus

Accumulative MEDCASE

Est

Periodic

Cost

OMA Cost:

Review Results

Study Objective:

To determine the incidence of rotavirus as a cause of gastroenteritis in our pediatric population. Also to determine if Rotazyme (R) should be available as a diagnostic tool in our Pathology Laboratory.

Technical Approach:

Thirty children with acute diarrhea will have stool samples tested for 1) Rotavirus with Rotazyme, 2) stool culture for bacterial pathogens (Salmonella, Shigella and Campylobacter), 3) Wright's stain for white cells.

Progress:

Nineteen stools from Pediatric patients were studied to determine the incidence of Rotavirus in acute diarrhea at William Beaumont Army Medical Center. Two (10.5%) were positive. No bacterial pathogens were identified in this small sample. We conclude that Rotavirus is a significant cause of diarrhea among Pediatric patients and that this procedure should be adopted by the Clinical Laboratory.

# Detail Summary Sheet

Date: 1 Oct 82      Prot No: 82/43      Status: Ongoing

## Title:

Adolescent Immunity to Varicella and Cytomegalovirus

Start Date:      Est Comp Date:

Principal Investigator:      Facility:

LTC M. Schydlower, MC

Dept/Sec: Dept Pediatrics      Assoc Investigators

## Key Words:

Varicella; Cytomegalovirus

Accumulative MEDCASE Cost	Est OMA Cost:	Periodic Review Results
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## Study Objective:

To determine the immune status of adolescents age 13-17 years to varicella and cytomegalovirus.

## Technical Approach:

Each year, May through August, days are set aside at WBAMC for school and sport physical examinations for military dependent children and adolescents as required by the local schools. Approximately 300 adolescents are examined on these days. Sera will be collected from approximately 150 adolescents and analyzed for seronegativity for varicella by complement fixation and neutralization tests. Sera will also be tested for cytomegalovirus by complement fixation and anticomplement immunofluorescence. The laboratory of Dr. Philip Brunell at the Department of Pediatrics, University of Texas Health Science Center, San Antonio, will test for varicella, and the laboratory of Dr. Martha Yow, Department of Pediatrics, Baylor University in Houston, will test for CMV. Both are experts in the study of these viruses. The data obtained will be correlated with age, sex, ethnic background, rank (as an index of economic background) and history of disease. Approximately 5 cc of blood will be obtained by venipuncture after obtaining appropriate informed consent.

## Progress:

Sera has been collected and is ready for shipment to testing facilities. We anticipate compilation of data and literature search by next summer.

# Detail Summary Sheet

Date: 1 Oct 82 Prot No: 82/45 Status: Ongoing

Title:

Use of VM-26 in Acute Leukemia

Start Date:

Est Comp Date:

Principal Investigator:

Facility:

Jerry J. Swaney, M.D., DAC

Dept/Sec: Dept Pediatrics

Assoc Investigators

Key Words:

VM-26; Leukemia

Accumulative MEDCASE

Est

Periodic

Cost

OMA Cost:

Review Results

Study Objective:

VM-26 will be used as remission induction agent and maintenance agent for refractory acute leukemia in children and adolescents. The response rate to VM-26 will be evaluated, as well as its toxicity.

Technical Approach:

Patients to be enrolled for this evaluation will be those children or adolescents with acute leukemia in relapse and refractory to other available chemotherapeutic agents. The number to be enrolled is unknown as this will vary with number of children and adolescents who relapse.

Attempts at induction of remission in refractory acute leukemia in bone marrow relapse will be undertaken with combination chemotherapy of intravenously administered VM-26 and cytosine arabinoside. After determination of hematologic relapse and evaluation of renal and hepatic function with standard laboratory tests chemotherapy will be instituted.

The patients will have prior to beginning therapy a bone marrow aspiration and biopsy, spinal tap, SMA 20, and CBC with platelets. A hemogram will be obtained prior to every course of therapy and an SMA-20 prior to every other course.

Intravenous chemotherapy will be semi-weekly for a total of eight courses. These will be administered on a Monday and Thursday or a Tuesday and Friday schedule for four consecutive weeks. A bone marrow aspiration will be done preceeding the first and fifth courses, and at the time a ninth course would be due.

**CHEMOTHERAPY PLAN:**

VM-26 will be given in combination with cytosine Arabinoside (Ara-C, Cytosar) for induction and maintenance therapy.

VM-26 165 mg/m<sup>2</sup> IV 2 times a week for 4 infusions and cytosine Arabinoside 300 mg/m<sup>2</sup> IV just prior to VM-26 2 times a week for four injections. The VM-26 will be mixed at 1 mg/cc in .05 D 1/3 NS to be infused over 30-60 minutes. The Ara-C will be mixed as per package instructions and given IV push.

Bone marrow aspiration and biopsy will be performed Day 15 to determine marrow status and cellularity. Evaluation of peripheral demogram, bone marrow status and patient status will determine if the chemotherapy is to be continued, or modified. Maintenance therapy will consist of the above regimen given every two weeks.

Data will be recorded on the hematology flow sheets currently in use. Copy of consent will be maintained in folder.

**Progress:**

This IND study is awaiting HSRRB approval.

# Detail Summary Sheet

Date:	1 Oct 82	Prot No:	82/49	Status:	Completed
Title:					
Study of the Effect of Ritalin (Methylphenidate) on Thyroid Function.					
Start Date:			Est Comp Date:		
Principal Investigator:			Facility:		
CPT Beatrice Ting, MC					
Dept/Sec:		Dept Pediatrics		Assoc Investigators	
Key Words:					
Ritalin; Thyroid function					

Accumulative MEDCASE	Est	Periodic
Cost	OMA Cost:	Review Results
Study Objective:		

Ritalin (methylphenidate) is being used extensively in the treatment of attention deficit disorder with dramatic to moderate effect on attention span, activity level and behavior. It has been shown that it can cause systolic blood pressure rise and increase in heart rate, but the effect of Ritalin on thyroid function, including the hypothalamus-thyroid gland axis, has never been looked into, to the best of my knowledge.

## Technical Approach:

Children in Developmental Clinic who are already on Ritalin, are to be included in the study. A random selection of up to fifty children, coming in for followup, would be asked to participate in the study. A consent will be obtained at the time of appointment, and a blood sample obtained approximately two hours after the Ritalin dosage. The child will be taken off Ritalin after that visit and another blood sample redrawn one week after summer vacation unless there are summer plans, i.e., long trips, day camp that entail a need for it). Another blood sample would be obtained one month after discontinuation of Ritalin if there has been an effect on thyroid studies with the first followup sample. A TSH, T3U, and T4 will be done on all samples and the means in the on and off drug samples will be compared by paired t-test. Serum will be saved for possible analysis of T3 by RIA, free T4 and free T3.

## Progress:

Data collection is complete and statistical analysis of the effect of Ritalin on thyroid function looking at T3U, T4, FTI and TSH showed no statistically significant changes on medication or off medication. There were two children with changes on and off medication who are being followed further and plans are to write the project as case reports and associated findings.

# Detail Summary Sheet

Date: 1 Oct 82	Prot No: 81/37	Status: Ongoing
Title: Torque and Its Relationship to Academic Achievement and Behavior in Children		
Start Date:	Est Comp Date:	
Principal Investigator:	Facility:	
MAJ T.B. Jeffrey, MSC		
Dept/Sec: Psychology Svc	Assoc Investigators	
Key Words: Torque	LTC P. LoPiccolo, MC Mr Thomas D. Carter, Jr, M.Ed	
Accumulative MEDCASE	Est	Periodic
Cost	OMA Cost:	Review Results
Study Objective:		

To evaluate the relationship between torque, academic achievement and behavior in children.

## Technical Approach:

One hundred children between the ages of 9 and 13 seen in the Pediatric Outpatient Clinic will be evaluated with the following instruments: Torque Test, Wide Range Achievement Test (Jastok, Bijour, and Jastok, 1963), Connor's Abbreviated Teacher Rating Scale, the Burk's Behavior Rating Scale, the Peabody Picture Vocabulary Test, and selected portions of Reitan's Lateral Dominance Examination.

The Peabody Picture Vocabulary Test correlates at a high level (Range = .63 - .87) with intelligence scales and requires only a few minutes to administer and score. Groups will be matched (torque versus nontorque) for level of intellectual functioning.

The results of the Torque Test will be scored by employing a single blind procedure. Data will be analyzed dichotomously (torque versus nontorque) to determine if a relationship exists between torque, lateral dominance, academic achievement, and behavior through a multivariate analysis of variance paradigm (2x3x2x2 factorial design). It is hypothesized that those with torque will display mixed lateral dominance on Reitan's test. It is also hypothesized that those with torque will do less well as measured by academic

achievement than their torque-free peers. A third hypothesis is that those with torque will have more behavioral problems as perceived by teachers and parents than their torque-free peers.

**Progress:**

Eighteen patients were entered into the study with no untoward occurrences. A PCS move by the senior associate investigator temporarily suspended collection of protocols. Based upon the current patient flow, we are expecting to complete the study by 1 Dec 1983, and anticipate no difficulties or untoward occurrences.



# Detail Summary Sheet

Date: 1 Oct 82 Prot No: 82/27 Status: Ongoing  
Title:

Low Back Pain and Return of Function Following Medical Intervention

Start Date: Est Comp Date:  
Principal Investigator: Facility:  
LTC T.B. Jeffrey, MSC

Dept/Sec: Dept Psychiatry Assoc Investigators  
Key Words:  
Low back pain

Accumulative MEDCASE Est Periodic  
Cost OMA Cost: Review Results  
Study Objective:

To compare selected outcome predictors of medical intervention for relief of low back pain (LBP).

## Technical Approach:

A minimum of 200 patients referred to neurosurgery and orthopedic surgery with LBP will be evaluated with a medical history, Cornell Medical Index (CI), A Pain Survey, and the MMPI. Predictions of treatment outcome will be made by the staff neurosurgeon, orthopedic surgeon, and psychologist at the time of the patient's initial presentation to each practitioner. Patients will be provided treatment as is judged appropriate by the staff. Prediction of treatment outcome will be evaluated approximately 60 days after medical intervention through medical review of the patient's response to treatment and a telephone/mail survey in which the patient provides data on relief of pain and/or return of function.

By analysis of covariance, the numerical predictory scales (MMPI), CI, Pain Survey, and Physical Findings) will be evaluated with the criterion variables (Operative/Diagnostic Findings, 60 Day Post Operative Treatment Response Scale) to determine the degree of predictability of any particular scale or combination of scales.

## Progress:

Eighteen patients have been entered into the study. Informed consent has not been obtained in all cases because the psychometric procedures employed are routine and would have been completed by the patient even if they were not going to be used as a part of this study.

# Detail Summary Sheet

Date: 1 Oct 1982 Prot No: 82/46 Status: Completed

Title:

Baseline MMPI Profile for an Active Duty Military Population

Start Date:

Est Comp Date:

Principal Investigator:

Facility:

MAJ G.R. Greenfield, MSC

Dept/Sec: Dept Psychiatry

Assoc Investigators

Key Words:

MMPI: Active duty population

Accumulative MEDCASE

Est

Periodic

Cost

OMA Cost:

Review Results

Study Objective:

To establish normals for the MMPI in an active duty military population to be used as a baseline for clinical MMPI interpretation.

## Technical Approach:

The groups of subjects will be administered three instruments; the MMPI, the Shipley Institute of Living Scale, and a demographic questionnaire. The materials provided to each subject will be numbered but will not be marked with any information which would specifically identify the subject. The Shipley Institute of Living Scale requires 20 minutes in which to be administered. It provides a reliable estimate of intelligence and verification of a reading level sufficient to validly take the MMPI. The demographic questionnaire will provide documentation of demographic characteristics of the population which is tested and will permit screening (and non-inclusion) of data from subjects with histories of psychiatric disorders. This is designed to ensure achieving a "normal" sample population.

Tabulations of the demographic questionnaires and scoring of the Shipley Institute of Living Scale records will be performed by the principal investigator. MMPI records from subjects with inadequate reading ability or a history of psychiatric disorders will be excluded from the sample from which norms will be computed.

## Progress:

Six hundred-seventy-nine patients were entered in the study with no untoward occurrences. Informed consent was obtained in all cases. The data collection from 679 subjects was completed and mailed to Walter Reed Army Medical Center, Psychology Service, for their analysis and publication. Final results will be published by WRAMC.

# Detail Summary Sheet

Date: 1 Oct 82 Prot No: 82/42 Status: Ongoing

## Title:

Clinical and Surgical Correlation Between Computerized Axial Tomography (CT) vs Metrizamide Myelography in the Patient with Low Back Pain.

## Start Date:

Est Comp Date:

Principal Investigator:

Facility:

CPT W.V. McAbee, MC

Dept/Sec: Dept Radiology

Assoc Investigators

## Key Words:

Low back pain; CT; Metrizamide myelography

Accumulative MEDCASE

Est

Periodic

Cost

OMA Cost:

Review Results

## Study Objective:

To compare which method (CT or metrizamide myelography) has the greatest degree of correlation with surgical and clinical findings in the low back patient and to determine the strengths and weaknesses of both modalities.

## Technical Approach:

The study will consist of 100 low back pain patients that would ordinarily receive a metrizamide lumbar myelogram at our institution and who subsequently go to surgery. Initially the patient will receive a lumbar CT scan.

1. Areas to be scanned will coincide with regions of clinical suspicion.
2. IV contrast will be given in bolus form of 100cc (Conray 60).
3. CT cuts at 5 mm thickness spaced at 5 mm distances from the bottom of the superior pedicles to the top of the inferior pedicles of the involved disc space.
4. The doctor performing the study will read the film routinely with available clinical information
5. The film will be read "blindly" by one of the clinical investigators without clinical information filling out the protocol CT form.

Metrizamide myelogram will follow the CT scan.

1. 15cc of 190 mg/cc of metrizamide will be injected into the subarachnoid space.
2. AP, lateral, oblique and cross table lateral decubitus films will be obtained.
3. The doctor performing the study will read out the film with all the clinical information available.
4. The film will be read by one of the clinical investigators without clinical information and he will fill out the protocol myelogram form.

Clinicians will be asked to fill out a clinical information sheet before the performance of any exam. The sheet should include: 1) probable levels of involvement, 2) degree of clinical suspicion, 3) brief history and pertinent physical findings, 4) the surgeon will be asked to comment on the nature of the surgical findings to include:

1. Nerve root impingement and type.

- Hypertrophied facet
- Hypertrophied ligamentum flavum
- Bulging disc
- Free fragment
- Other

2. Amount of saline injected into involved disc.
3. Did he find what he expected on the basis of the CT and myelogram at surgery.

Progress:

Patient accrual began near the end of FY82 on this long-term project.

# Detail Summary Sheet

Date: 1 Oct 81 Prot No: 78/03 Status: Ongoing

Title:

National Intraocular Lens Implantation Study

Start Date:

Est Comp Date:

Principal Investigator:

Facility:

MAJ Donald J. Bergin, MC

Dept/Sec: Surgery, Ophthalmology

Assoc Investigators

Key Words:

Intraocular lens

Accumulative MEDCASE

Est

Periodic

Cost

OMA Cost:

Review Results

Study Objective:

To participate in the study of clinical results of implantations of intraocular lens organized by the Intraocular Lens Manufacturer's Association in response to directives of the Ophthalmic Classification Panel, FDA.

Technical Approach:

An intraocular lens is a prosthetic replacement for the eye's crystalline lens. It is placed in the eye at the time of cataract surgery, where it is fixated by a variety of means, with the intention that it remain permanently and correct the large refractive error remaining after conventional cataract surgery.

Progress:

The annual review of this protocol was conducted Sept 82. Eighty-three additional operations were performed between 1 Jul 81 and 1 Jul 82. Two-hundred thirty-seven operations have now been performed since the initial approval of the protocol and the first operation on 22 Nov 1977. The following complications were reported this period:

(1) A 60-year-old female underwent intraocular implantation of the right eye 1 Oct 81. On the first post-operative day the lens was noted to be of improper fit. The patient was returned to the operating room 2 Oct 81 where the implant was removed. As a result of vitreous loss at the time of the second surgery, when an anterior vitrectomy was performed, the patient suffers from cystoid macular edema, which causes a significant loss in her central vision. Peripheral vision is good.

(2) A 68-year-old male underwent intraocular lens implant of the left eye on 11 Aug 81. On the second postoperative day the lens was noted to be of improper fit and the patient was returned to surgery with replacement of the intraocular lens being carried out. The patient did well following this and was discharged to outpatient care.

(3) A 61-year-old female underwent implantation of intraocular lens on the left eye 6 Jan 81 (2.b. last year's report). On 4 Mar 82 the patient underwent removal of the intraocular lens, left eye, due to chronic iritis secondary to the implant. The patient has continued to do poorly in the left eye. She is being air evacuated to Brooke Army Medical Center on 3 Sep 82 for further evaluation of epithelial ingrowth in the left eye. Prognosis at this time is poor.

(4) A 61-year-old female who underwent intraocular lens implant of the right eye 30 Mar 78 has done well in the ensuing years. Lens implanted was a CILCO Sputnik. In Jan 81 the patient began having problems with corneal decompensation of the right eye. She was treated conservatively with slow progression of the corneal edema. In Aug 82 the patient had stromal and bullous edema. On 25 Aug 82 the patient was taken to the operating room to undergo a corneal transplant of the right eye and removal of the intraocular lens implant. The patient is doing well at this time.

(5) A 76-year-old female underwent intraocular lens implant of the right eye in 1976. A CILCO Sputnik lens was implanted. The patient has done well in the ensuing years. Approximately 5-6 months ago the patient noted decrease in the vision in the right eye. The patient was treated conservatively until recently when pseudophakia bullous keratopathy became severe and the patient underwent a corneal transplant with removal of the intraocular lens on 8 Aug 82. The patient did well postoperatively and is being treated on an outpatient basis.

# Detail Summary Sheet

Date: 1 Oct 81      Prot No: 80/12      Status: Completed

## Title:

Effect of Systemic Anti-Neoplastic Chemotherapy on Dacron Graft Incorporation

Start Date:

Est Comp Date:

Principal Investigator:

Facility:

David O. Rauls, PhD

Dept/Sec:

Assoc Investigators

Key Words:

Thoracoabdominal aortic graft;  
Platelet survival time

LTC J.T. Collins, MC  
LTC T.J. Brown, DO

Accumulative MEDCASE  
Cost

Est  
OMA Cost: \$39(16,868)

Periodic  
Review Results

Study Objective:

To determine the effect of systemic cancer chemotherapy on the healing events which allow incorporation and formation of a neointima in dacron prosthetic grafts.

## Technical Approach:

Graft incorporation will be followed by platelet survival times. This is an accepted measure of graft incorporation with platelet survival being reduced by fifty percent immediately after graft placement and returning to normal as the graft is incorporated. Also dogs will be sacrificed at six weeks and six months for histological examination of graft healing. Any dogs which die or develop complications related to the graft will be histologically studied. Graft incorporation will be studied in the following settings: (1) A graft placed simultaneously with initiation of chemotherapy. (2) A graft placement after initiation of chemotherapy. Three controls will be used. In one group platelet survival will be followed without any treatment, to monitor consistency of technique of platelet survival determination. In another group platelet survival will be monitored before and during chemotherapy. A third group will have a thoracoabdominal graft placed without chemotherapy.

## Progress:

Publications and presentations to date from this study have been listed in the tables in this and previous Annual Progress Reports. A current manuscript submitted for publication further summarizes a portion of the work.

Five groups of adult beagle dogs of both sexes were used. Platelet survival times were determined for each animal prior to entering a treatment regimen. These pre-treatment values are reported as time zero values. Additional platelet survival times were determined for each animal corresponding to approximately seven days, 30 days, 90 days and at 90-day intervals thereafter post-initiation of any form of treatment (surgery or drug administration). Treatment groups were followed for at least one year.

Platelet survival times were determined using indium-111 oxine labeled autologous platelets as described in detail elsewhere. Platelets were isolated by differential centrifugation, suspended in isotonic saline, mixed at room temperature with about 100 uCi of indium-111 oxine (Medi-Physics, Inc., Emeryville, CA) and allowed to stand at room temperature for 15-30 minutes. After washing and resuspension in autologous plasma, the platelets were reinjected into the animal. Blood samples were taken at 0.5 hr, 2 hr, 24 hr, and at 24 hr intervals with the final sample taken 96 hrs post-injection. Radioactivity in the samples was counted in a gamma counter (Beckman 4000) optimized for counting indium-111.

Values were normalized to the 0.5 hr sample and mean platelet survival times were calculated as recommended by the International Committee on Standardization in Hematology using the multi-hit model for platelet disappearance from circulation.

Six to nine dogs were assigned to each treatment group. Group 1 consisted of a control group of animals for which platelet survival times were determined at intervals corresponding to those of the treatment groups. Group 2 received a treatment regimen of doxorubicin (1.5 mg/kg i.v. on day 1 and every three weeks thereafter for a total of four doses). Group 3 underwent surgery for placement of thoracoabdominal aortic bypass grafts of woven Dacron<sup>R</sup> as described by Clagett *et al.* The animals in Group 4 also received an aortic bypass graft on day 1 and ninety days post-surgery a treatment regimen of doxorubicin (1.5 mg/kg i.v. on day 90 and every three weeks thereafter for a total of four doses) was initiated. In Group 5 the doxorubicin regimen was started on day 1 and completed as above. Ninety days after initiation of the drug treatment, aortic bypass grafts were placed.

The dogs that underwent replacement of the thoracoabdominal aorta received grafts of woven Dacron<sup>R</sup> which were approximately 10mm in diameter and 28-36 cm in length. The proximal anastomosis was end-to-side at the level of the inferior pulmonary vein. The aortic prosthesis was routed behind the left hemidiaphragm to the retroperitoneal site of the distal end-to-side aortic anastomosis below the renal arteries. The thoracic aorta was ligated just below the proximal anastomosis with an umbilical tape, thus shunting all aortic blood through the prosthesis. Anesthesia was induced with sodium pentothal and maintained with halothane. All animals received ampicillin pre- and post-operatively for prophylaxis against infection.



## Statistical methods

Within the control group and each treatment group, analysis was done on the mean platelet survival times (hrs) of animals grouped by days into the study. Day zero identifies a response as being pre-treatment. These sample means are point estimates of population means which were estimated by 95% confidence intervals based on the t-distribution. No pooling was done here concerning variance estimates. Within each treatment group, comparison is made between the pre-treatment group and each day group by a paired t-test with each dog serving as his own control. This tests the null hypothesis of no treatment effect at a particular day. The standard paired t-test based on the average difference score was modified to include in the variance estimate the independent estimate based on the one-way analysis of variance by dog in the control group. The variance of a difference score was estimated by twice the control group mean square within dogs and is valid with the assumption of independent errors. This modified paired t-test has increased degrees of freedom.

## RESULTS

There was considerable animal to animal variability in platelet survival times as evidenced by the size of the 95% confidence interval for the mean in the control group (Fig 1). However, platelet survival times remained relatively constant over a 270 day period for each animal resulting in little change in the control group means over the 270 day period. Methodology for determining platelet survival times and variability in the analysis have been discussed in detail elsewhere.

Doxorubicin was found to dramatically reduce platelet survival in dogs within one week of initiation of treatment (Fig 1, Group 2). Survival times were significantly different from pre-treatment levels at one week and four weeks post-initiation of treatment. Significant thrombocytopenia did not develop during drug treatment ( $p < 0.05$ , paired t-test). Recovery was rapid with platelet kinetics returning to normal within three weeks of cessation of treatment.

Dacron<sup>R</sup> graft placement resulted in greatly reduced platelet survival times with slow recovery over a period of months (Fig 2, Group 3). Administration of doxorubicin ninety days after graft installation resulted in delayed recovery of platelet kinetics (Fig 2, Group 4). The data for the first 90 days after initiation of treatment (i.e. 180 days into the study) indicate an acute direct effect of doxorubicin on platelet survival and do not accurately reflect graft incorporation. As demonstrated, recovery is rapid (Group 2) and data collected at the 190 day point and thereafter should reflect graft incorporation.

Initiation of doxorubicin administration 90 days prior to surgery also resulted in delayed return of platelet survival to baseline, again presumably reflecting delayed graft incorporation (Fig 3, Group 5). At one year post surgery the platelet survival

times were still significantly different from baseline levels.

#### DISCUSSION

The acute effects of doxorubicin on platelet kinetics were unanticipated (Fig 1). Platelet function, as measured by a variety of in vitro tests, is affected by a number of drugs. The anti-tumor drugs doxorubicin and daunomycin are structural congeners and share some clinical and toxic properties. Both are concentrated by platelets relative to plasma at doses used clinically.

Doxorubicin has been shown to increase human platelet lipid peroxidation, presumably altering membrane unsaturated fatty acids. The effect of lipid peroxidation on in vivo platelet function has not been evaluated. Daunorubicin has been shown to inhibit collagen and thrombin-induced platelet aggregation in a concentration dependent manner in vitro.

The effects seen in this study could result from a broad range of possible actions of doxorubicin. Whether the alteration of platelet kinetics is a direct effect on the platelet, a possibility suggested by in vitro studies, or is the result of alterations in the body's platelet clearance mechanisms is not known. Further research is necessary in order to provide a sound explanation for this observation.

Clagett et al. found that platelet kinetics in dogs with aortic thoracoabdominal Dacron<sup>R</sup> grafts did not return to normal until 18 months after surgery. Our results indicate a somewhat more rapid recovery of platelet kinetics (Fig 2). The difference in the time required for recovery in our group of dogs, as compared to the previously reported results, is possibly due to the difference in the population of dogs used or differences in methodology.

Initiation of the doxorubicin treatment regimen (1.5 mg/kg i.v. every three weeks for a total of four doses) 90 days after placement of the graft was intended to give an idea of the effect of the drug on graft incorporation. At 90 days post-surgery the animal has overcome the acute effects of the surgery but the graft has not become fully infiltrated by neointima as evidenced by a platelet survival time that is still reduced. Interpretation of the results (Fig 2) must take into account the acute effect of doxorubicin on platelet kinetics. Initiation of the drug treatment regimen at 90 days post-surgery and consideration of the effects of doxorubicin on platelet kinetics prevents statistical comparison of platelet survival times prior to 180 days. However, the platelet survival times remain depressed for 288 days (Fig 2) which is long past the time required for recovery from the acute effects of doxorubicin. It is apparent then that doxorubicin delays the rate of recovery of platelet kinetics to normal following placement of a dacron graft with recovery being incomplete at 288 days post-surgery while animals receiving grafts but not exposed to doxorubicin recovered by 273 days (Fig 2).

Initiation of doxorubicin administration 90 days prior to surgery was intended to give information concerning the existence of persistent effects of the drug on the ability of the graft to become

incorporated. Platelet survival times remained significantly depressed at 483 days post-initiation of drug administration. This is 393 days post-surgery, indicating that doxorubicin administration prior to installation of an aortic bypass graft affected those factors responsible for recovery of platelet kinetics.

The data presented here demonstrate that doxorubicin has an acute effect on platelet survival in vivo which is readily reversible upon cessation of drug treatment. The drug was also shown to delay return of platelet survival times to pre-treatment levels when treatment was initiated 90 days after graft placement. This indicates that the drug in some manner delays the development of a neointimal layer within the graft. The delayed recovery was not dramatically different from the surgery only group. However, these results do indicate that doxorubicin affects the incorporation of Dacron<sup>R</sup> grafts.

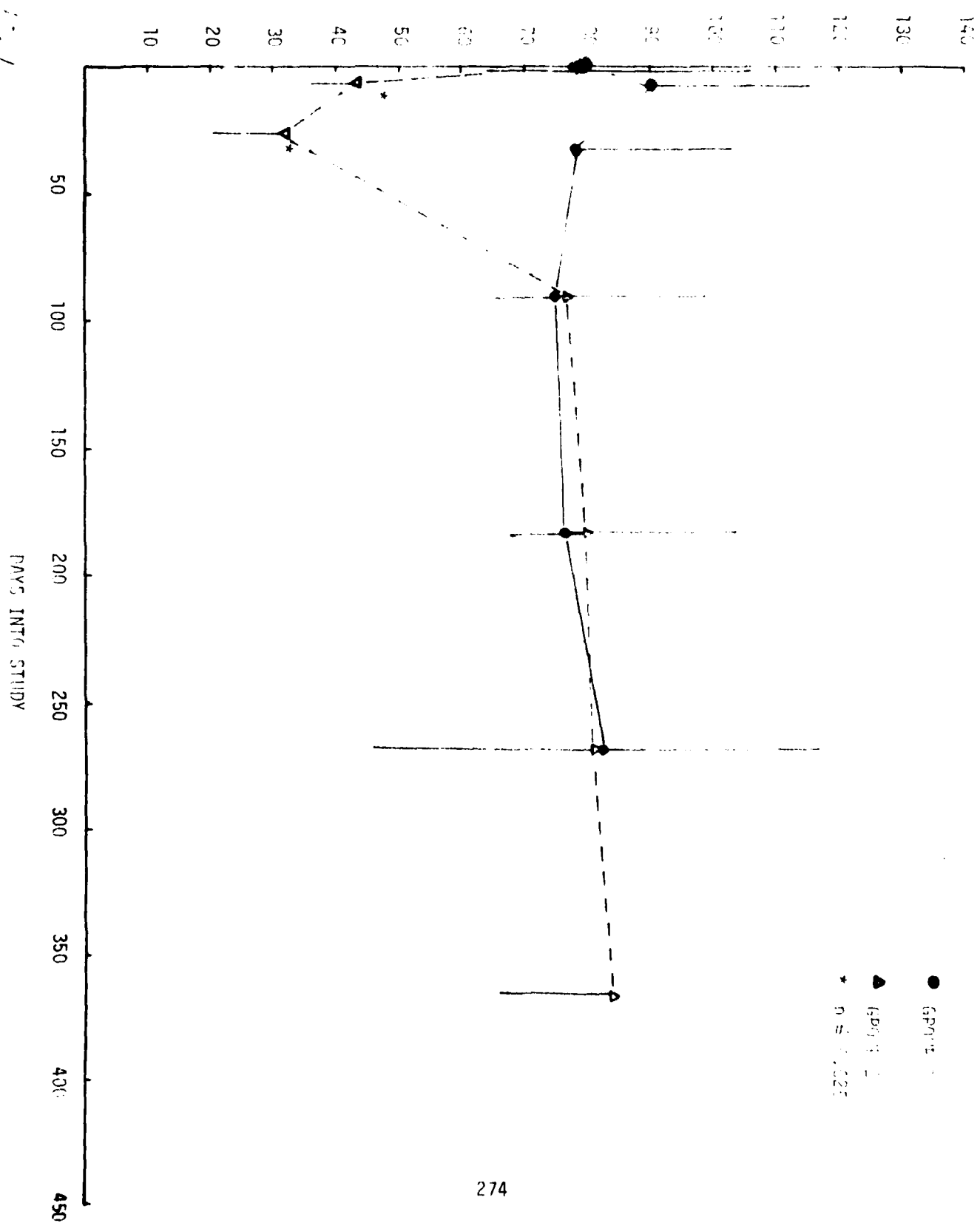
Doxorubicin treatment prior to graft installation also results in prolonged graft incorporation times. The effect is difficult to explain. Doxorubicin clears from the blood rapidly and is distributed to the tissues. Elimination follows a slow time course. It is possible that effects on various tissues are evident long after plasma concentrations have become very low.

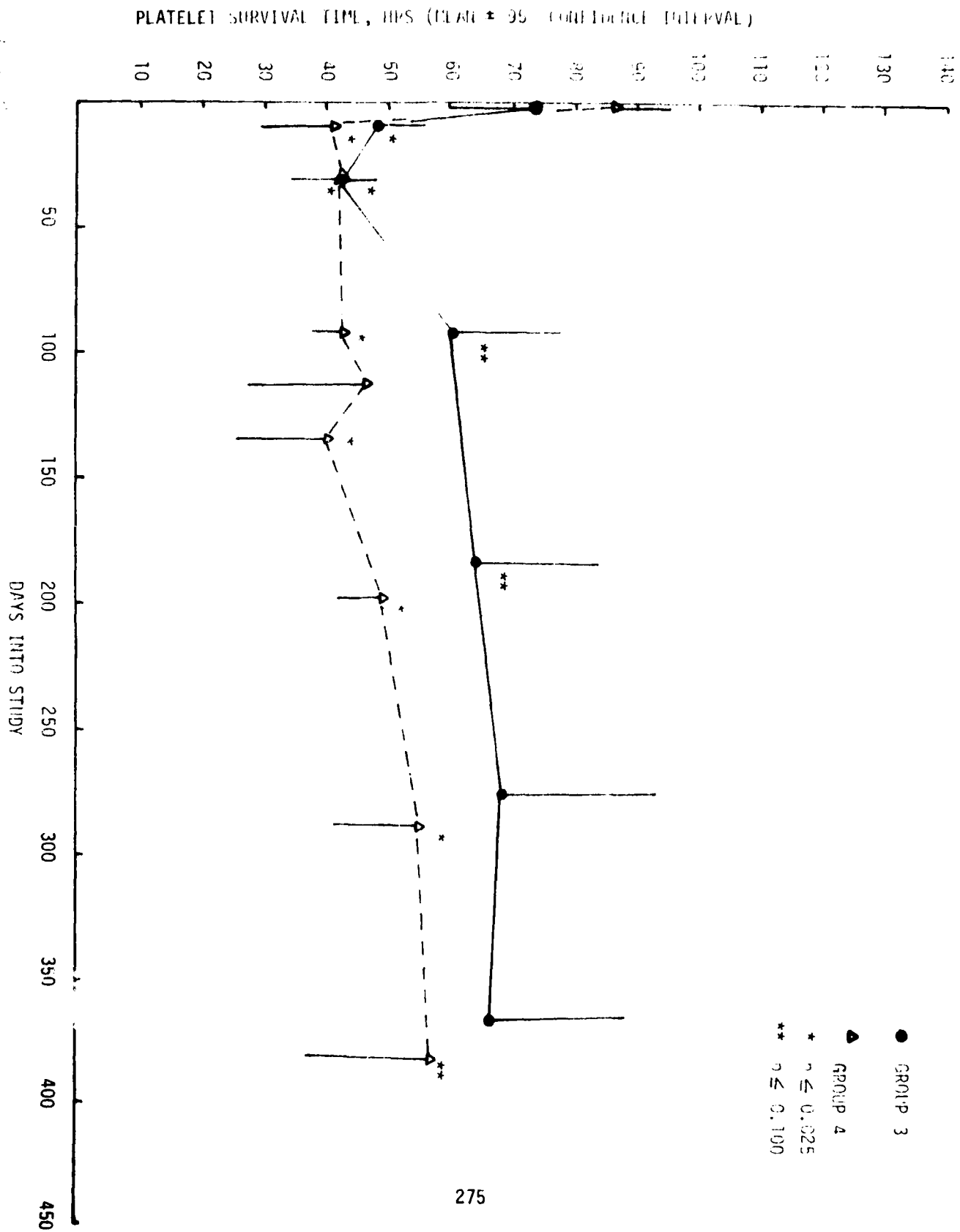
In conclusion, the finding that doxorubicin dramatically alters platelet kinetics in vivo in the absence of thrombocytopenia indicates that the drug has acute effects on the platelet itself or on platelet removal mechanisms. The ability of doxorubicin to delay Dacron<sup>R</sup> graft incorporation as indicated by delayed recovery of platelet survival times, whether given before or after surgery, is not well understood. Further work is needed in order to determine how seriously the results noted here affect the clinical situation.

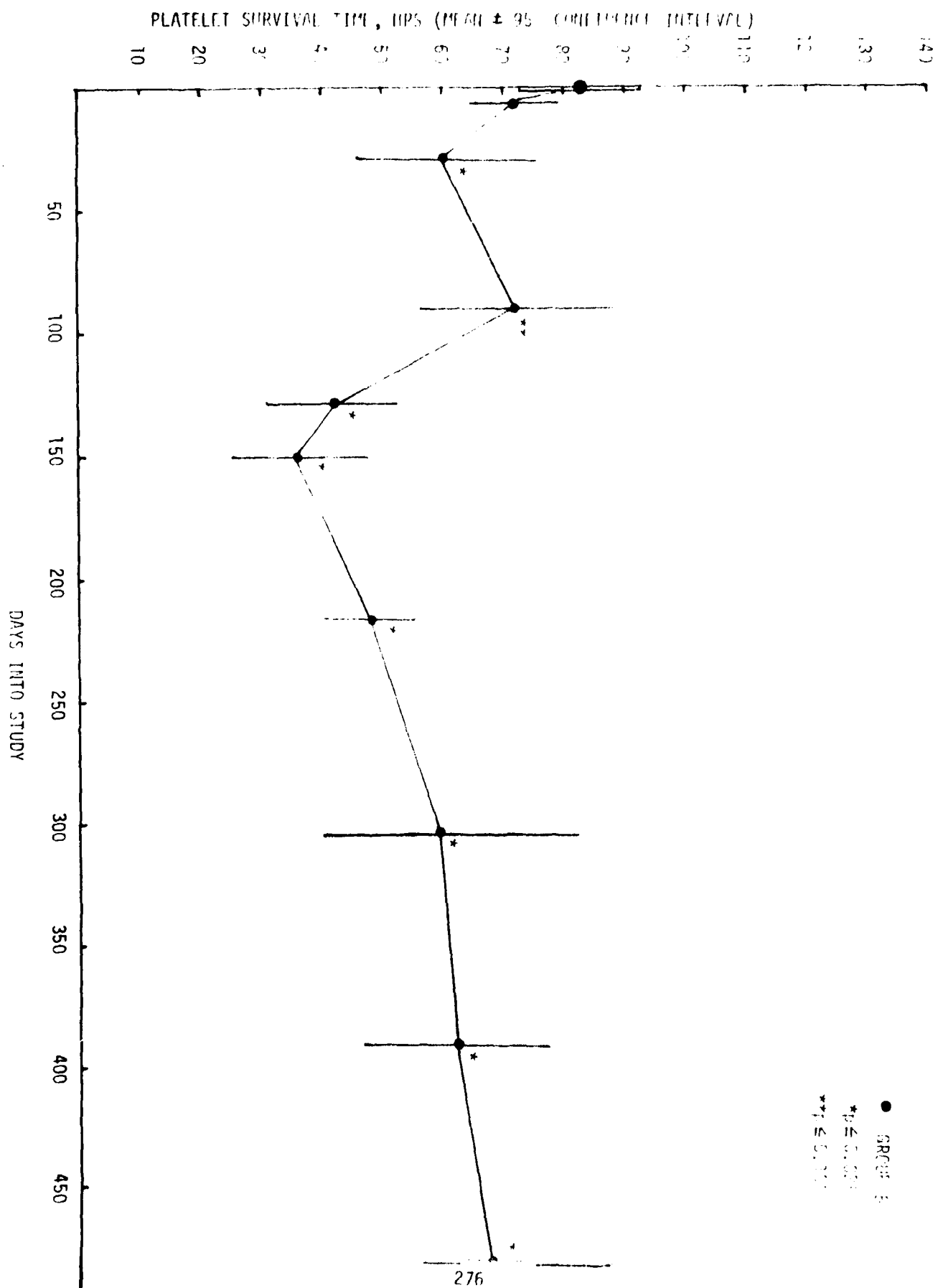
## LEGENDS

- FIG 1: Change in platelet survival with time. Group 1 (n=6)- control, Group 2 (n=7)- doxorubicin treated.
- FIG 2: Change in platelet survival with time. Group 3 (n=7)- graft installation alone, Group 4 (n=8)- graft installation followed by doxorubicin treatment 90 days post-surgery.
- FIG 3: Change in platelet survival with time. Group 5 (n=9)- Doxorubicin treatment followed by graft installation 90 days later.

PLATELET SURVIVAL TIME, HRS (MEAN  $\pm$  95% CONFIDENCE INTERVAL)







# Detail Summary Sheet

Date: 1 Oct 82 Prot No: 81/02 Status: Ongoing

## Title:

Replacement of the Infra-Renal Inferior Vena Cava with an Improved Expanded Polyfluorotetraethylene (e-PTFE) Graft and Comparison of Two Graft

Start Date:

Est Comp Date:

Principal Investigator:

Facility:

CPT T.E. Gaines, MC

Dept/Sec: Surgery

Assoc Investigators

Key Words:

Vena cava; PTFE vascular grafts

LTC S. Cabellon, MC

Accumulative MEDCASE

Est

Periodic

Cost

OMA Cost: \$750(750)

Review Results

Study Objective:

To evaluate an improved e-PTFA(IMRA) graft in the infra-renal vena cava in dogs. Parameters studied will be those of initial pressure, flow characteristics, and patency. Histologic appearance will also be studied should thrombosis or occlusion occur. The effect of graft diameter is to be compared for two graft sizes, one smaller than, and one approximating, the diameter of the native vessel. Our goal is to work toward development of the reliable grafting procedure and prosthetic material for replacing important veins in humans.

Technical Approach:

Dogs will be used as the animal model. It is intended to use the optimum synthetic material and grafting procedure in this study and to test the material and procedure in the most difficult situation. Therefore, an A-V fistula will be employed and anticoagulation will be considered at the time of the procedure. The hemodynamic effect of the A-V fistula will be monitored with blood flow and pressure studies. The graft material will be e-PTFE which has a pore size of approximately 30 microns. The graft will have rigid external support consisting of a spiral of solid teflon. The length of the graft will be 6 cm so as to provide a length that has clinical utility. In addition to the above considerations the effect of velocity of flow will be studied with this experiment. Two graft sizes will be used, one being 8 mm and approximating the native size of the inferior vena cava in the dog, the other, 5 mm, being narrower. Presumably flow does not decrease through the narrower



graft (an assumption to be measured in the study). The velocity of flow would be higher than through the larger graft. The effect of this higher velocity of flow may be to improve patency and this will be monitored.

**Progress:**

The first four animals have been studied. The start of this protocol was delayed due to lack of space, but will progress as time, space, and personnel allow.

# Detail Summary Sheet

Date: 1 Oct 82      Prot No: 81/07      Status: Ongoing

Title:  
Comparison of Mortality and Morbidity of Uretero-  
ileocecosigmoidostomy With Other Urinary Diversions.

Start Date:      Est Comp Date:

Principal Investigator:      Facility:

COL F.L. Diaz-Ball, MC

Dept/Sec:      Surgery      Assoc Investigators

Key Words:  
Ureteroileocecosigmoidostomy

Accumulative MEDCASE Cost	Est OMA Cost: 1210(1210)	Periodic Review Results
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Study Objective:

At present, the urinary diversion methods accepted as effective have been the ones which require an external appliance over a stoma and on occasion ureterosigmoidostomy. Examples among these are: The ileal loop or conduit of Bricker, ileocecal loop, or the colonic loop. All these are prone to complications and are less ideal. In 1972 the senior investigator and associates reported on a study in dogs done at Letterman Army Medical Center in which the feasibility of an internal diversion using a uretero-ileocecosigmoidostomy was established. The anti-reflux action of the ileo-cecal valve can be enhanced with the newly developed Zinman technique. Prior to a wide application in humans, we should prove that the incidence of complications is comparable or preferably less than the accepted methods used at this time. It is projected to perform surgery in control groups of ileal loops, colonic loops, ureterosigmoidostomies and compare incidence of complication with equal numbers of uretero-ileo-cecosigmoidostomies.

Technical Approach:

1. Control Group I - a series of 6-12 dogs will undergo ileal loop diversion.
2. Control Group II - a series of 6-12 dogs will undergo a colonic loop.
3. Control Group III - a series of 6-12 dogs will undergo a ureterosigmoidostomy.

4. Tested Group IV - a series of 6-12 dogs will undergo uretero-ileocecocolostomies.

**Data Collection:**

**Preoperative:** Will include serum creatinine, BUN, and CBC. Urine C and S if possible, IVP and R.C. Barium enemas would be performed to establish functional integrity of urinary and bowel tracts including ileocecal valve competence. Kidney biopsy for regular and electron microscopy. **Intra-operative:** serum creatinine, BUN, urine from renal pelvis or ureters for C and S, urine aspirates from bladder for C and S.

**Postoperative:** Every 1-2 weeks BUN and creatine. Every month an IVP, and every 2 months a cystogram. Will be as in humans with IVs until safe to feed, etc. At least every 1-2 weeks repeat CBC, BUN, creatinine, retrograde cystogram every month times 3 and then every 3 months times 3.

**Long Term:** Dogs will be kept ideally at least one year alive, facilities permitting. At that time they could be sacrificed, autopsied for detection of changes due to surgery in the urinary system and other systems.

Control groups I and III, and the test group will comprise the initial study. If time and funding permit, control group II, and possibly another group with ileo-cecal cutaneous diversion, may be compared to the tested group.

**Progress:**

Twelve animals have been entered and are undergoing follow-up examinations as per protocol. Personnel and space constraints in the Biologic Research Facility continued to slow progress..

Detail Summary Sheet

Date: 1 Oct 82      Prot No: 82/26      Status: Ongoing  
Title:  
Early or Delayed Surgery for Acute Cholecystitis: A Controlled  
Randomized Study

Start Date:      Est Comp Date:  
Principal Investigator:      Facility:  
LTC S. Cabellon, MC      WBAMC

Dept/Sec:      Assoc Investigators  
Key Words:

Cholecystitis, treatment      COL Daniel G. Cavanaugh, MC

Accumulative MEDCASE Cost	Est OMA Cost:	Periodic Review Results
Study Objective:		

To compare early and delayed surgery in the management of acute cholecystitis from the standpoint of complications of surgery, duration of the operative procedure, misdiagnosis of the disease and length of hospital stay.

Technical Approach:

Patients with acute cholecystitis diagnosed clinically with the help of ultrasound and cholescintigraphy will be randomly treated surgically either early or delayed. The benefit of each treatment mode will be assessed in terms of the complications of surgery, duration of the operative procedure, misdiagnosis of the disease and length of hospital stay.

Progress:

Six patients have been entered. Informed consent was obtained in all cases. There have been no untoward occurrences. The numbers of patients in the study are too small as yet to determine the trend of the study.

Detail Summary Sheet

Date: 1 Oct 82      Prot No: 82/40      Status: Ongoing  
Title:

Prospective Evaluation of the Abdominal Aorta in Peripheral Vascular Patients by Ultrasound

Start Date: 1 June 82      Est Comp Date: FEB 83  
Principal Investigator:      Facility:

LTC S. Cabellon

WBAMC

Dept/Sec: Dept Surgery/Peripheral Vascular Assoc Investigators  
Key Words:

Abdominal Aorta, Ultrasound

Accumulative MEDCARE      Est      Periodic  
Cost      ONA Cost:      Review Results  
Study Objective:

To determine whether the prospective evaluation of the aorta in patients with peripheral vascular disease will uncover a high incidence of undiagnosed abdominal aortic aneurysms. If the incidence is high, then it must be recommended that all patients with peripheral vascular disease should, as part of their routine followup or initial evaluation, undergo an ultrasound examination.

Technical Approach:

Ultrasound examination of the abdominal aorta on patients with atherosclerotic peripheral vascular disease after determining whether their aorta is palpable or nonpalpable.

Progress:

Seventy-three patients have been entered. Informed consent was obtained in all cases. There have been no untoward occurrences. The results are presently being tabulated and organized; preliminary report will be presented at the 10th Vascular Conference, USVHS, Bethesda, MD 2-3 Dec 1982.

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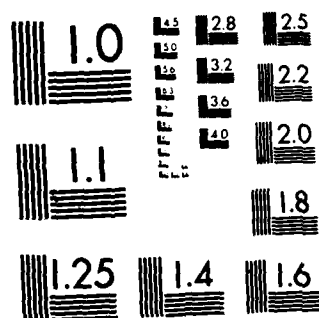
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